Exhibit 93, part 3

evaluated included: chromium electroplating facilities; welding in construction; metal cutting operations on chromium-containing materials in ship breaking; chromate-paint removal with abrasive blasting; atomized alloy-spray coating; foundry operations; printing; and the manufacture of refractory brick, coloured glass, prefabricated concrete products, and treated wood products. Personal breathing zone samples (full-shift and short-term) and general area samples were collected. Results were compared to the NIOSH recommended exposure limit (REL) of 1 μg/m^3 (for a 10-hour exposure). Full-shift personal exposures to chromium (VI) were in the range of 3.0–16 μg/m^3 at the electroplating facilities, and 2.4–55 μg/m^3 at a painting and coating facility that used products containing chromium (VI) (Blade *et al.*, 2007).

NIOSH conducted a health hazard evaluation of worker exposures during the welding and manufacturing of stainless steel products and fabricated piping systems. Personal breathing zone air sampling concentrations of chromium (VI) were above the NIOSH REL. The highest concentrations for nickel and chromium (VI) occurred during welding operations inside large stainless steel pipes (0.26 mg/m^3 and 0.36 mg/m^3), and while welding fins on a large stainless steel pipe (Hall *et al.*, 2005).

As part of an international epidemiological study of workers in the pulp and paper industry, Teschke *et al.* (1999) assembled and analysed 7293 previously unpublished exposure measurements collected in non-production departments from 147 mills in 11 countries. Chromium (VI) compounds were reported in 26 time-weighted average (TWA) samples from nine mills, with a mean airborne chromium (VI) concentration of 63 μg/m^3 (range, 0.04–1220 μg/m^3).

Proctor *et al.* (2003) analysed more than 800 measurements of airborne chromium (VI) from 23 surveys conducted during 1943–71 at a chromate production plant in Painesville, Ohio, USA. The highest chromium (VI) concentrations recorded at the plant occurred in shipping (e.g. bagging of dichromate), lime and ash, and filtering operations (maximum yearly TWA concentrations of 8.9, 2.7, and 2.3 mg/m^3, respectively). The data showed that concentrations in the indoor operating areas of the plant generally decreased over time, dropping from 0.72 mg/m^3 in the 1940s, to 0.27 mg/m^3 in 1957–64, and to 0.039 mg/m^3 in 1965–72.

In a study to assess industry compliance with existing and proposed standards, Lurie & Wolfe (2002) conducted a secondary data analysis of 813 chromium (VI) measurements collected in 1990–2000 by OSHA. Chromium (VI) was not detected in 436 measurements. In the remaining samples, the median 8-hour TWA concentration was 10 mg/m^3 (n = 197; range, 0.01–13960 mg/m^3), and the median ceiling concentration was 40.5 mg/m^3 (n = 180; range, 0.25–25000 mg/m^3). In the plating and polishing industry, the median 8-hour TWA concentration was 8.2 mg/m^3 (n = 65; range, 0.01–400 mg/m^3), and the median ceiling concentration was 23 mg/m^3 (n = 51; range, 1–410 mg/m^3).

Luippold *et al.* (2005) examined the mortality of two cohorts of chromate production workers constituting the current US chromium chemical industry, after engineering controls were implemented. Personal air monitoring sampling for chromium (VI) at the two plants resulted in approximately 5230 personal air-monitoring measurements taken during 1974–88 for Plant 1, and 1200 measurements taken during 1981–98 for Plant 2. Personal levels of chromium (VI) exposure were very low at both plants (geometric mean, < 1.5 μg/m^3 for most years; range of annual means, 0.36–4.36 μg/m^3). At both plants, the work areas with the highest average exposures were generally less than 10 μg/m^3 for most years.

In an occupational exposure study of chromium in an aircraft construction factory, personal airborne samples were collected in a group of 16 workers over a 4-hour period, and urinary samples were collected from 55

workers at the beginning of their work shift (on Monday), and at the beginning and end of their work shift (on Friday). The geometric mean air concentration was 0.17 μg/m^3 (GSD, 5.35 μg/m^3; range, 0.02–1.5 μg/m^3). Geometric mean creatinine levels were as follows: pre-shift Monday, 0.63 μg/g (GSD, 0.53 μg/g; range, 0.23–2.9 μg/g); pre-shift Friday, 0.95 μg/g (GSD, 0.94 μg/g; range, 0.25–4.8 μg/g); and post-shift Friday, 0.91 μg/g (GSD, 1.38 μg/g; range, 0.16–7.7 μg/g) (Gianello *et al.*, 1998).

2. Cancer in Humans

2.1 Introduction

A large number of case reports dating to the late 19th and early-to-mid-20th centuries raised suspicions that workers in various industries with exposure to chromium compounds, including chromate production, production of chromate pigments and chromium plating may be at risk of developing various cancers (Newman, 1890; Pfeil, 1935; Teleky, 1936; IARC, 1990). Beginning in the mid-20th century, cohort studies were undertaken in these industries as well as in some other occupations and industries with potential exposure to chromium compounds, such as ferrochromium or stainless steel production, welding, leather tanning, and some others. By the 1980s considerable evidence had accumulated on cancer risks of chromium-exposed workers, and leading to the identification of chromium (VI) compounds as a human carcinogen (IARC, 1990).

The strongest evidence presented at the time concerned the lung. There was weaker and less consistent evidence of effects on gastrointestinal sites, mainly stomach, and some reports of excess risks at several other organs, such as pancreas, prostate and bladder. Furthermore, there were some case reports and small clusters of nasal or sinonasal cavity cancers in workers exposed to chromium (VI). Based on the review of the previous *IARC Monograph*, and on a subsequent review of relevant epidemiological evidence accumulated since then, the Working Group focused the current review on those sites for which the evidence indicates possible associations with chromium (VI) compounds, namely: lung, nose, and nasal sinus. Because of recent controversy regarding possible effects on stomach cancer (Proctor *et al.*, 2002; Beaumont *et al.*, 2008), the Working Group also reviewed relevant evidence for this organ. For other organs, the number of reports of excess risks is unremarkable in the context of the numbers of studies that have been conducted, and thus they have not been reviewed.

There have been at least 50 epidemiological studies that could be informative about cancer risks related to chromium (VI). Many of the studies have given rise to multiple reports; sometimes these simply represent follow-up updates, but often the different reports also present different types of analyses of subgroups or of case–control analyses within a cohort. Only a minority of the studies contain documented measurements of chromium (VI) exposure, particularly measurements that pertain to the era of exposure of the workforce that was investigated. It was therefore necessary to select and present the evidence according to the availability of relevant exposure information. The studies were triaged into the following categories:

1. Cohort studies in industries in which workers were highly likely to have been exposed at relatively high levels. This included workers in chromate production, chromate pigment production, and chromium electroplating.
2. Cohort studies in which workers were possibly exposed to relatively high levels but not with the same degree of certainty or concentration as those in category a. This included stainless steel welders.
3. Other studies in which workers may have been exposed to chromium (VI), but with lower likelihood or lower frequency or lower

concentrations than workers in categories 1) and 2). Among the occupations/industries in this category were ferrochromium and stainless steel production, mild steel welding, general paint production, general spray painting, tanneries, gold mining, and nickel plating.

Studies in category 3) were not routinely included in the current review because there were sufficiently informative studies in categories 1) and 2), except if the authors presented information indicative of exposure to non-negligible levels of chromium (VI).

Most of the informative evidence comes from industry-based cohort studies, some of which have been complemented by nested case–control analyses. One of the main limitations of industry-based cohort studies is the usual absence of information on smoking and other potential confounders aside from age, sex, and race. Nonetheless, except for some case–control studies of nasal cancer, the Working Group relied on cohort studies to provide informative results.

For each study selected, the Working Group chose the most recent publication; occasionally there were results in earlier papers that were also deemed important to present here. Further, in each publication there are typically a large number of results presented by organ site, by demographic characteristics of workers, by some index of duration or dose of exposure, and sometimes by analysing the data in a nested case–control fashion. For the purposes of the current review, the Working Group selected the key results from each publication, typically including the most general result available for workers exposed to chromium (VI) as well as a result for a subgroup characterized by relatively high duration or dose of exposure, when there were enough numbers in such a category.

2.2 Cancer of the lung

Almost all of the relative risk estimates for cancer of the lung presented in Table 2.1 (available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-04-Table2.1.pdf) are greater than 1.0. Among chromate production workers, virtually all studies showed excess risks of lung cancer, except for a few estimates of risks for US workers hired since exposures were lowered (Luippold *et al.*, 2005), but these latter analyses had few subjects and low power.

Similarly, studies of chromate pigment production workers tended to show elevated risks of lung cancer in nearly all the cohorts and subcohorts reported, though not every relative risk estimate was statistically significant. Also, among chromium electroplating workers, there was a clear pattern of excess risks in most cohorts. Workers in other industries who may have had somewhat lower levels of chromium (VI) exposure than those in the previously mentioned industries, had a less convincing set of relative risk estimates, though nearly all were above 1.0.

A few of the cohort studies collected high-quality smoking histories, and incorporated these into nested case–control analyses; these tended to show elevated risks independent of smoking. Several other studies had collected partial or representative smoking frequencies among their workers, and for most of these studies, the main results were unlikely to have been meaningfully confounded by smoking patterns in the workers.

A recent meta-analysis estimated an overall standardized mortality ratio (SMR) of 1.41 (95%CI: 1.35–1.47) for lung cancer among 47 studies of workers with possible chromium (VI) exposure (Cole & Rodu, 2005). [The Working Group noted that because of the great difficulty in establishing equivalencies between different studies in terms of the types and levels of exposures to chromium (VI), the summary estimates are difficult to interpret. Further, it appears

that some of the study populations in that meta-analysis overlapped with each other.]

In aggregate, the results continue to show that exposure to chromium (VI) increases the risks of lung cancer.

Very few of the epidemiological studies provided results relating to specific chromium (VI) compounds. Workers in chromate production were likely to have been exposed to mixtures of sodium, potassium, calcium and ammonium chromates and dichromates; the highest and most consistent excess risks were observed in these cohorts. Workers in chromate pigment production and spray painting were likely to have been exposed to zinc and/or lead chromates, also resulting in high risks. Steel smelting and welding probably resulted in exposure to alkaline chromates, and risks reported in these cohorts tended to be less clear than among the chromate producers and the chromate pigment producers. Because there seemed to be increased risks in diverse industries involving exposure to a variety of chromium (VI) compounds of varying solubilities, this observation argues for a general carcinogenic effect of chromium (VI).

2.3 Cancer of the nose and nasal sinus

Cancer of the nose and nasal sinus is extremely rare, the incidence of which is roughly 1/100th of the incidence of cancer of the lung (Parkin *et al.*,1997). In fact, most cohorts of workers exposed to chromium (VI) do not report on of the incidence of nose and nasal sinus cancers. [The Working Group noted that this could mean there were none in the cohort or that the investigators did not examine and report it.]

Table 2.2 (available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-04-Table2.2.pdf) shows the nine (ten studies including Sorahan *et al.*, 1987) cohort studies that did report how many nasal cancers occurred. Combining those nine (ten) cohorts, there were mentions of 22 (25) cases of nasal or nasal sinus cancer. For the four cohorts that reported an expected as well as an observed number of cases, the aggregate was 12 observed and 1.5 expected giving an SMR of 8.0. Because several cohort studies failed to report any cases, it is difficult to integrate the appropriate observed and expected numbers from these studies into the overall estimate of risk from cohort studies. [The Working Group believed that many of the studies which made no report on nasal cancer actually had none.]

Case reports since the 1960s have reported 11 (12 including one case reported in Enterline, 1974) cases of nasal or nasal sinus cancer among chromate workers. Without any indication of person-years at risk, it is difficult to infer whether this represents an excess.

There have been three informative case–control studies on nasal and nasal sinus cancer. Two showed some indications of excess risk among workers with possible exposure to chromium (VI) compounds, but the study with the best exposure assessment protocol (Luce *et al.*, 1993) reported no excess risks for workers exposed to chromium (VI).

In aggregate, the epidemiological evidence remains suggestive but inconclusive regarding the effect of chromium (VI) on nasal and nasal sinus cancers. [The Working Group noted that systematic confounding by nickel exposure is unlikely in the cohorts presented in Table 2.2 online.]

2.4 Cancer of the stomach

There is little evidence of an association between exposure to chromium (VI) and cancer of the stomach; there are as many point estimates above 1.0 as there are below. There has been concern about possible hazards related to the ingestion of chromium (VI) in drinking-water, and one study in the People's Republic of China

(Zhang & Li, 1987) and a subsequent reanalysis of the Chinese data (Beaumont *et al.*, 2008) seem to indicate a somewhat elevated risk of stomach cancer in which drinking-water was heavily polluted by a ferrochromium plant. However, one single ecological study does not constitute rigorous evidence of an association between exposure to chromium (VI) and cancer of the stomach.

See Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-04-Table2.3.pdf.

2.5 Synthesis

The large majority of informative cohort studies indicate that there is an excess risk of lung cancer among workers exposed to chromium (VI), particularly in chromate production, chromate pigment production, and chromium electroplating. It is unlikely that any biases or chance can explain these findings.

There are some case reports, cohort studies and case–control studies that suggest a possible excess of cancer of the nose and nasal sinus among workers exposed to chromium (VI). However, this evidence is susceptible to publication and reporting biases because many of the cohort studies did not report on nasal cancers, and it is not clear how to evaluate the significance of the case reports.

There is little evidence that exposure to chromium (VI) causes stomach or other cancers.

3. Cancer in Experimental Animals

Chromium (VI) compounds have been tested for carcinogenicity by several routes in several animal species and strains (IARC, 1990), and the following paragraphs summarize some key findings from previous IARC evaluations of chromium (VI) compounds.

Calcium chromate induced lung tumours in mice (males and females combined) when given by inhalation (Nettesheim *et al.*, 1971) and local tumours when given by intramuscular administration (Payne, 1960). In rats it caused lung tumours (adenoma, squamous cell carcinoma, or adenocarcinoma) when given by intratracheal administration (Steinhoff *et al.*, 1986) or intrabronchial administration (Levy & Venitt, 1986), bronchial (carcinomas or squamous cell carcinomas) when administered by intrabronchial administration (Levy *et al.*, 1986), and local tumours in rats treated by intrapleural (Hueper, 1961; Hueper & Payne, 1962) or intramuscular administration (Hueper & Payne, 1959, 1962; Hueper, 1961; Roe & Carter, 1969).

Lead chromate (and its derived pigments), administered by subcutaneous injection (Maltoni, 1974, 1976; Maltoni *et al.*, 1982) or intramuscular injection cause malignant tumours at the site of injection and renal tumours (Furst *et al.*, 1976) in rats. Subcutaneous administration of basic lead chromate caused local sarcomas in rats (Maltoni, 1974, 1976; Maltoni *et al.*, 1982). In rats, zinc chromates caused bronchial carcinomas when administered by intrabronchial implantation (Levy *et al.*, 1986), and local tumours when given intrapleurally (Hueper, 1961), subcutaneously (Maltoni *et al.*, 1982) or intramuscularly (Hueper, 1961). Strontium chromate also caused bronchial carcinomas (intrabronchial implantation administration) (Levy *et al.*, 1986), and local sarcomas (intrapleural and intramuscular administration) in rats (Hueper, 1961).

Chromium trioxide when tested as a mist by inhalation caused nasal papillomas in mice (Adachi & Takemoto, 1987). Local tumours were observed in rats exposed to sintered chromium trioxide (Hueper & Payne, 1959). A low incidence of lung adenocarcinomas was induced after inhalation of chromium trioxide, and some lung tumours were observed in rats exposed by intrabronchial administration but neither were

statistically significant (Adachi *et al.*, 1986; Levy *et al.*, 1986; Levy & Venitt, 1986).

Sodium dichromate (when given by inhalation or intratracheal administration) caused lung tumours (benign and malignant) (Glaser *et al.*, 1986; Steinhoff *et al.*, 1986) in rats.

3.1 Studies published since the previous *IARC Monograph*

Since the previous *IARC Monograph* (IARC, 1990), studies in experimental animals have been conducted to evaluate oral exposure to chromium (VI). Table 3.1 summarizes the results of these studies, and the text below summarizes the major findings for each specific compound.

3.1.1 Sodium dichromate dihydrate

The National Toxicology Program (NTP) conducted 2-year drinking-water studies of sodium dichromate dihydrate in male and female B6C3F$_1$ mice, and in male and female F344 rats. In rats, sodium dichromate dihydrate significantly increased the incidence of squamous cell epithelium tumours of the oral mucosa or tongue in the high-dose groups (516 mg/L) of males and females. Trend analysis indicated a dose–response relationship in both males and females. In mice, sodium dichromate dihydrate significantly increased tumours (adenomas or carcinomas) of the small intestine (duodenum, jejunum, or ileum) in the two-highest dose groups of males (85.7 and 257.4 mg/L) and females (172 and 516 mg/L). Dose–response relationships were observed in both sexes (NTP, 2008).

3.1.2 Potassium chromate

Davidson *et al.* (2004) studied the effects of potassium chromate on ultraviolet(UV)-induced skin tumours in female hairless mice (CRL: SK1-hrBR). Mice were exposed to UV alone, various concentration of potassium chromate alone (given in the drinking-water), and UV together with various concentrations of potassium chromate. Administration of drinking-water containing potassium chromate did not induce skin tumours alone. However, chromate treatment significantly increased the multiplicity of UV-induced skin tumours, and the multiplicity of malignant UV-induced skin tumours. Similar results were found in male and female hairless mice (Uddin *et al.*, 2007). The analysis of skin indicated that UV treatment increased the level of chromium in the exposed skin (Davidson *et al.*, 2004).

3.2 Synthesis

The administration of calcium chromate in mice and sodium dichromate in rats by inhalation caused lung cancer. Calcium chromate and sodium dichromate administered by intratracheal instillation caused lung cancer in rats. Intratracheal administration of calcium chromate, zinc chromate, and strontium chromate caused lung cancer in rats. Several chromium compounds by repository injection (calcium chromate, lead chromate, zinc chromate, strontium chromate) caused local sarcomas. Oral administration of sodium dichromate to rats and mice caused cancer of the oral cavity and of the gastrointestinal tract. Potassium chromate given orally, although not given alone, enhanced UV-induced skin carcinogenesis, indicating tumour systemic effects.

Table 3.1 Studies of cancer in experimental animals exposed to chromium (VI) (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance[a]	Comments
Sodium dichromate dihydrate				
Rat, F344/N (M, F) 2 yr NTP (2008)	Drinking-water 0, 14.3, 57.3 172, 516 mg/L Average daily doses: M-0, 0.6, 2.2 6, 17 mg/kg bw F-0, 0.7, 2.7, 7, 20 mg/kg bw *ad libitum* 50/group/sex	Oral mucosa (squamous cell carcinomas):[b] M–0/50, 0/50, 0/49, 0/50, 6/49 (12%) F–0/50, 0/50, 0/50, 2/50 (4%), 11/50 (22%) Tongue (squamous cell papillomas or carcinomas): M–0, 1, 0, 0, 1 F–1, 1, 0, 1, 0 Oral mucosa or tongue:[c] M–0/50, 1/50 (2%), 0/49, 0/50, 7/49 (14%) F–1/50 (2%), 1/50 (2%), 0/50, 2/50 (4%), 11/50 (22%)	M: $P < 0.05$ (high dose); $P_{trend} < 0.001$ F: $P < 0.001$ (high dose); $P_{trend} < 0.001$ M: $P < 0.01$; $P_{trend} < 0.001$ F: $P < 0.01$ (high dose); $P_{trend} < 0.001$	Age at start, 6–7 wk 99.7% pure No treatment effects on survival Decreased bw in high-dose males and females Decreased water consumption of the 2 highest doses
Mouse, B6C3F$_1$ (M, F) 2 yr NTP(2008)	Drinking-water M: 0, 14.3, 28.6, 85.7, 257.4 mg/L F: 0, 14.3, 57.3, 172, 516 mg/L Average daily doses: M–0, 1.1, 2.6, 7, 17 mg/kg bw F–0, 1.1, 39.9, 9, 25 mg/kg bw *ad libitum* 50/group/sex	Small intestine (adenomas): M–1/50 (2%), 1/50 (2%), 1/50 (2%), 5/50 (10%), 17/50 (34%) F–0/50, 1/50 (2%), 2/50 (4%), 15/50 (30%), 16/50 (32%) Small intestine (carcinomas): M–0/50, 2/50 (4%), 1/50 (2%), 3/50 (6%), 5/50 (10%) F–1/50 (2%), 0/50, 2/50 (4%), 3/50 (6%), 7/50 (14%) Small intestine (adenomas or carcinomas):[d] M–1/50 (2%), 3/50 (6%), 2/50 (4%), 7/50 (14%), 20/50 (40%) F–1/50 (2%), 1/50 (2%), 4/50 (8%), 17/50 (34%), 22/50 (44%)	M: $P < 0.001$ (high dose); $P_{trend} < 0.001$ F: $P < 0.001$ (2 highest doses); $P_{trend} < 0.001$ M: $P < 0.05$ (high dose); $P_{trend} < 0.05$ F: $P < 0.05$ (high dose); $P_{trend} < 0.001$ M: $P < 0.001$ (high dose), $P < 0.05$ (85.7 mg/L), $P_{trend} < 0.001$ F: $P < 0.001$ (2 highest doses 172 and 516 mg); $P_{trend} < 0.001$	Age at start, 6–7 wk 99.7% pure No treatment effects on survival Decreased body weight in 2 highest female dose groups Decreased water consumption of the 2 highest doses (males and females) Most of the tumours were located in the duodenum

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance[a]	Comments
Potassium chromate (K_2CrO_4)				
Mouse, CRL: Sk1-hrBR (F) 224 d Davidson *et al.* (2004)	Group 1: Controls Group 2: UV only Group 3: 2.5 ppm K_2CrO_4 Group 4: 5 ppm K_2CrO_4 Group 5: UV +0.5 ppm K_2CrO_4 Group 6: UV + 2.5 ppm K_2CrO_4 Group 7: UV + 5 ppm K_2CrO_4: UV: 1 mo after K_2CrO_4 1.1 kJ/m² 3 d/wk for 3 mo, followed by 1 wk break, and 1.3 kJ/m², 2 d/wk for 3 mo K_2CrO_4: 182 d, added to drinking-water every 7–10 d 120 animals	Skin (tumours): Groups 1, 3, 4–no tumours *Number of tumours (> 2mm/no of mice at 182 d):* Group 2–12/15 (0.8) Group 5–16/12 (1.39) Group 6–50/19 (2.63) Group 7–94/19 (5.02)	Group 6 vs Group 2, $P < 0.05$ Group 7 vs Group 2, $P < 0.01$	Age at start, 6 wk Chromium-only treatment had no effects on bw or toxicity Levels of chromium were measured in dorsal thoracic skin and abdominal skin in Groups 1, 4, and 7 UV + chromium had significantly higher chromium levels in back and underbelly skin

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance[a]	Comments
Mouse, CRL: Sk1-hrBR (M, F) 224 d Uddin *et al.* (2007)	Groups: treatment, *n* Group 1a: UV, 10 Group 1a: UV + 2.5 ppm K_2CrO_4, 10 Group 1c: UV + 5 ppm K_2CrO_4, 10 Group 2a: UV + 5 ppm K_2CrO_4, 10 Group 2b: UV + 5 ppm K_2CrO_4 + Vitamin E, 10 Group 2c: UV + 5 ppm K_2CrO_4 + selenium, 10 Mice administered K_2CrO_4 in drinking-water at 3 wk of age. 3 wk later UV treatment (1.0 kJ/m^2) 3 d/wk for 26 wk Vitamin E: 62.5 IU/kg Selenium: 5 mg/kg Group 1–males, Group 2–females (30/group)	Skin (number of tumours/mice at 26 wk): M– Group 1a: 1.9 ± 0.4 Group 1b: 5.9 ± 0.8 Group 1c: 8.6 ± 0.9 F– Group 2a: 3.9 ± 0.6 Group 2b: 3.5 ± 0.6 Group 2c: 3.6 ± 0.6	Group 1b vs 1a, $P < 0.001$ Group 1c vs 1a, $P < 0.0001$	Age, 3 wk Chromium had no effect on growth of the mice. Chromium levels in skin increased with dose Chromium also decreased the time until appearance of first tumours in males

[a] *P*-values for calculated by Poly 3- for NTP studies, which accounts for differential mortality in animals that do not reach terminal sacrifice.
[b] Historical control incidence for 2-yr drinking-water studies with NTP-20000 diet: M: 0/300, F: 0/300.
[c] Historical control incidence for 2-yr drinking-water studies with NTP-20000 diet: M: 2/300, range 0 to 2%; F: 3/300, range 0 to 2%.
[d] Historical control incidence for 2-yr drinking-water studies with NTP-20000 diet: M:11/299, range 0–10%; F: 4/350, range 0 to 4%.
[e] Borneff *et al.* (1968) published in German.
[f] No information on tumour incidence of this group was reported by Sedman *et al.* (2006).
[g] Two-Tailed Fisher Exact Test; Authors stated significant but did not provide*P*-value.
[h] Untreated and chromium only, controls not included since no tumours were observed in the study by Davidson *et al.* (2004).
bw, body weight; d, day or days; F, female; M, male; mo, month or months; UV, ultraviolet; vs, versus; wk, week or weeks; yr, year or years

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

In humans, the absorption, retention, and elimination of chromium compounds after exposure by inhalation depend on the solubility and particle size of the particular compound inhaled (for an extensive review, see ATSDR, 2008b). The retention may range from several hours to weeks. Inhaled chromium (VI) is readily absorbed from the respiratory tract. The degree of absorption depends on the physical and chemical properties of the particles (size, solubility), and the extent of reduction of the hexavalent form to chromium (III), which is absorbed to a much lesser extent. Thus, after intratracheal instillation in rats, 53–85% of chromium (VI) compounds with a particle size < 5 μm are absorbed into the bloodstream, with higher absorption rates in case of more soluble compounds; the rest remains in the lungs. For comparison, absorption of chromium (III) from the respiratory tract is only 5–30% (ATSDR, 2008b). The same factors mentioned above apply to absorption from the gastrointestinal tract, although absorption by this route is generally much less compared with that in the respiratory tract. Average absorption fractions determined in human volunteers for chromium (III) or chromium (VI) were reported as 0.13% or 6.9%, respectively. Chromium (VI) can penetrate human skin to some extent (ATSDR, 2008b).

In humans and rodents, absorbed chromium (VI) is distributed in nearly all tissues, with the highest concentrations found in the kidney, liver, and bone. Studies conducted by the NTP in male rats and female mice orally exposed to chromium (VI) for 2 years showed dose-related and time-dependent increases in total chromium concentrations in red cells, plasma, and in several organs. The total chromium content of the red cells was higher than that of plasma. The concentration of total chromium in the forestomach was found to be markedly higher in mice than in rats (NTP, 2008).

Within the human body, chromium (VI) undergoes a series of reduction steps to form the thermodynamically stable chromium (III). When reduction occurs extracellularly, this process can be considered as detoxification because the cell membrane is a nearly impermeable barrier for chromium (III). The remaining chromium (VI) is present as a mixture of chromate (CrO_4^{2-}) and hydrochromate ($HCrO_4^-$); because water-soluble chromates are iso-structural with sulfate and phosphate ions, they are readily taken up by sulfate channels. In case of poorly water-soluble chromates, particles of < 5 μm can be phagocytosed, and gradually dissolved intracellularly. Within the cell, chromium (VI) is reduced stepwise to chromium (III), giving rise to reactive intermediates as well as DNA and protein adducts. In blood, chromium (VI) is taken up into red blood cells, is reduced, and then bound to proteins. After exposure by inhalation, excretion occurs predominantly via the urine. Due to the low absorption of chromium compounds from the gastrointestinal tract, the major pathway of elimination after oral exposure is through the faeces (ATSDR, 2008b).

4.2 Genetic and related effects

The oxidation state of chromium is the most important factor when considering its biochemical activity (Beyersmann & Hartwig, 2008; Salnikow & Zhitkovich, 2008). Chromium (VI), but not chromium (III) compounds, have been shown to exert genotoxicity both *in vivo* and *in vitro*.

Lymphocytes of workers exposed to dusts of chromium (VI) compounds showed elevated frequencies of DNA strand breaks (Gambelunghe *et al.*, 2003), sister chromatid exchange (Wu *et al.*, 2001), and micronuclei (Vaglenov *et al.*, 1999; Benova *et al.*, 2002).

After intratracheal instillation in rats, chromium (VI) induced DNA strand breaks in lymphocytes (Gao *et al.*, 1992). After intraperitoneal injection of chromium (VI) to mice, micronuclei were induced in bone marrow. In contrast, no micronucleus induction was observed after oral administration, indicating that chromium (VI) does not reach the target cells to a high extent by this route of exposure (De Flora *et al.*, 2006). Chromium (VI) induces dominant lethal mutations in male mice (Paschin *et al.*, 1982).

In vitro, soluble chromium (VI) compounds are mutagenic in mammalian and bacterial test systems (De Flora *et al.*, 1990).

4.2.1 DNA damage

Chromium (VI) is unreactive towards DNA under physiological conditions. According to the uptake–reduction model originally established by Wetterhahn *et al.* (1989), chromium (VI) undergoes a series of reduction steps in cells, to form the thermodynamically stable chromium (III). Intracellular reduction does not require enzymatic steps but is mediated by direct electron transfer from ascorbate and non-protein thiols, such as glutathione and cysteine. During the reduction process, variable amounts of chromium (V) and chromium (IV) as well as organic radical species are generated; their exact nature, however, depends largely on the reducing species (Wetterhahn & Hamilton, 1989). Furthermore, comparative in-vivo and in-vitro studies revealed a major impact of the intracellular reductants on the nature and biological consequences of the resultant DNA lesions.

The major intracellular reductant under physiological conditions appears to be ascorbate, reaching millimolar concentrations in human tissues, and accounting for about 90% of chromium (VI) reduction reactions *in vivo* (Standeven *et al.*, 1992). In contrast, only micromolar concentrations of ascorbate are usually present in cell cultures (Quievryn *et al.*, 2002), which leads to an increase in thiol-mediated chromate reduction. When ascorbate is the reductant, two electrons are transferred, and chromium (IV) but not chromium (V) is generated as the first intermediate, whereas with cysteine as a reductant, predominantly chromium (V) is formed due to one-electron transfers (Stearns & Wetterhahn, 1994). In both cases, the final product is chromium (III), which reacts to produce different types of DNA lesions.

DNA lesions generated after exposure to chromium (VI) include chromium (III)–DNA adducts, DNA–protein and DNA–DNA interstrand crosslinks, DNA breaks as well as several oxidative DNA–base modifications. The predominant form of chromium (III)–DNA adducts are ternary adducts, where chromium forms a link between DNA and small molecules such as cysteine, histidine, glutathione or ascorbate, presumably arising from preformed chromium–ligand complexes during the reduction process. These adducts are formed primarily at phosphate groups, but the subsequent partial formation of chelates involving the phosphate group and the N^7-position of guanine have been suggested. Chelates formed from chromium–ascorbate particularly are potent premutagenic DNA lesions (Zhitkovich *et al.*, 2001).

The formation of DNA–protein crosslinks after chromate exposure is well established, but is estimated to account for less than 1% of chromium–DNA adducts. Biological consequences are likely to be disturbances of DNA replication and transcription. The formation of DNA–DNA crosslinks appears to be restricted to certain in-vitro conditions, due to severe steric hindrance upon intercalation of octahedral chromium (III) complexes (Zhitkovich, 2005).

DNA single-strand breaks may arise due to the reaction of chromium (V) with hydrogen peroxide, forming hydroxyl radicals. Nevertheless, if ascorbate is the predominant reductant under in-vivo conditions, the generation of chromium (V) and thus, single-strand

breaks, appears to be of minor importance (Quievryn *et al.*, 2003). Cytogenetic alterations in chromium (VI)-exposed cells in culture and *in vivo*, such as increased frequencies of chromosomal breaks and micronuclei, are suggested to be due to DNA double-strand breaks, produced by a cell-replication-dependent mechanism in the G2 phase of the cell cycle. Recent evidence suggests the involvement of mismatch repair in the formation of double-strand breaks. Thus, highly mutagenic ascorbate–chromium–DNA adducts lead to the error-prone repair of double-strand breaks through non-homologous end-joining. Furthermore, they induce mismatches during replication, leading to aberrant mismatch repair. Based on these findings, a model has been created to show that chronic exposure to toxic doses of chromium (VI) provokes the selective outgrowth of mismatch-repair-deficient clones with high rates of spontaneous mutagenesis, and thus, genomic instability (Reynolds *et al.*, 2007; Salnikow & Zhitkovich, 2008). In support of this model, chromium-induced cancers in exposed workers were associated with microsatellite instability and exhibited the loss of expression of MLH1, which is one of the essential mismatch-repair proteins (Takahashi *et al.*, 2005).

4.2.2 Oxidative stress

In the reduction of chromium (VI) to chromium (III) by cellular reductants, potentially toxic intermediates (oxygen radicals, sulfur radicals, and chromium radicals) are generated (Yao *et al.*, 2008). In a cell-free system, chromium (VI) reacted with glutathione to form chromium (V) and thiyl radicals (Wetterhahn *et al.*, 1989). Furthermore, after reduction of chromium (VI) by glutathione, chromium (V) can undergo Fenton-type reactions, producing hydroxyl radicals (Shi *et al.*, 1994), and 8-oxoguanine in isolated DNA (Faux *et al.*, 1992). In cultured mammalian cells, chromium (VI) induced the formation of superoxide and nitric oxide (Hassoun & Stohs, 1995). The administration of chromium (VI) to animals, which have higher tissue levels of ascorbate compared with cultured cells, did not induce the formation of 8-oxoguanine (Yuann *et al.*, 1999). This may be due to the lack of chromium (V) formation when ascorbate is the predominant reducing agent.

4.2.3 Further potentially relevant mechanisms

Besides direct genotoxic effects of chromium (VI) metabolites, chromate may activate various mitogen-activated protein kinases as well as transcription factors involved in inflammation and tumour growth. Nevertheless, because these effects have been observed in cell-culture systems and no distinct effects of chromium (VI) on cell proliferation have been shown, the relevance of these observations remains unclear at present. Perhaps of higher impact are the aneugenic properties of chromium (VI). Chronic treatment with lead-chromate particles induced neoplastic transformation of human bronchial cells, which was accompanied by centrosome amplification, and an increase in aneuploid metaphases (Xie *et al.*, 2007).

4.3 Synthesis

Several mechanisms are involved in the carcinogenesis induced by chromium (VI) that include the induction of DNA damage, the generation of oxidative stress and aneuploidy, leading to cell transformation. With respect to DNA damage, the spectrum of induced lesions appears to depend strongly on the cellular reductant involved. Thus, under physiological conditions with ascorbate as the major reductant, the generation of premutagenic ternary chromium–ascorbate–DNA adducts appears to be of major relevance, which may be linked to the increased number of mismatch-repair-resistant cells observed in chromate-induced lung tumours.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of chromium (VI) compounds. Chromium (VI) compounds cause cancer of the lung. Also positive associations have been observed between exposure to Chromium (VI) compounds and cancer of the nose and nasal sinuses.

There is *sufficient evidence* in experimental animals for the carcinogenicity of chromium (VI) compounds.

Chromium (VI) compounds are *carcinogenic to humans (Group 1).*

References

Adachi S & Takemoto K (1987). Occupational lung cancer. A comparison between humans and experimental animals *Sangyo Igaku*, 29: 345–357. PMID:2831418

Adachi S, Yoshimura H, Katayama H, Takemoto K (1986). Effects of chromium compounds on the respiratory system. Part 4. Long-term inhalation of chromic acid mist in electroplating to ICR female mice*Sangyo Igaku*, 28: 283–287. PMID:3784105

ATSDR (2000). *Chromium (TP-7)* In: *Toxicological Profile.* US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, pp. 461.

ATSDR (2008a). *Chromium (TP-7)* In: *Toxicological Profile.* US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, pp. 610.

ATSDR (2008b) *Toxicological Profile for Chromium.* Available at: http://www.atsdr.cdc.gov/toxprofiles/tp7.html#bookmark09

Beaumont JJ, Sedman RM, Reynolds SD *et al.* (2008). Cancer mortality in a Chinese population exposed to hexavalent chromium in drinking water. *Epidemiology*, 19: 12–23. doi:10.1097/EDE.0b013e31815cea4c PMID:18091413

Benova D, Hadjidekova V, Hristova R *et al.* (2002). Cytogenetic effects of hexavalent chromium in Bulgarian chromium platers. *Mutat Res*, 514: 29–38. PMID:11815242

Beyersmann D & Hartwig A (2008). Carcinogenic metal compounds: recent insight into molecular and cellular mechanisms. *Arch Toxicol*, 82: 493–512. doi:10.1007/s00204-008-0313-y PMID:18496671

Blade LM, Yencken MS, Wallace ME *et al.* (2007). Hexavalent chromium exposures and exposure-control technologies in American enterprise: results of a NIOSH field research study. *J Occup Environ Hyg*, 4: 596–618. doi:10.1080/15459620701463183 PMID:17577750

Borneff J, Engelhardt K, Griem W *et al.* (1968). Carcinogens in water and soil. XXII. Experiment with 3,4-benzopyrene and potassium chromate in mice drink *Arch Hyg Bakteriol*, 152: 45–53. PMID:5707368

CAREX Canada (2011). Available at: http://www.carexcanada.ca/en/chromium_%28hexavalent%29/occupational_exposure_estimates/phase_2/

Cole P & Rodu B (2005). Epidemiologic studies of chrome and cancer mortality: a series of meta-analyses. *Regul Toxicol Pharmacol*, 43: 225–231. doi:10.1016/j.yrtph.2005.06.009 PMID:16099572

Davidson T, Kluz T, Burns F *et al.* (2004). Exposure to chromium (VI) in the drinking water increases susceptibility to UV-induced skin tumors in hairless mice. *Toxicol Appl Pharmacol*, 196: 431–437. doi:10.1016/j.taap.2004.01.006 PMID:15094314

De Flora S, Bagnasco M, Serra D, Zanacchi P (1990). Genotoxicity of chromium compounds. A review. *Mutat Res*, 238: 99–172. PMID:2407950

De Flora S, Iltcheva M, Balansky RM (2006). Oral chromium(VI) does not affect the frequency of micronuclei in hematopoietic cells of adult mice and of transplacentally exposed fetuses. *Mutat Res*, 610: 38–47. PMID:16872865

Ellis AS, Johnson TM, Bullen TD (2002). Chromium isotopes and the fate of hexavalent chromium in the environment. *Science*, 295: 2060–2062. doi:10.1126/science.1068368 PMID:11896274

Enterline PE (1974). Respiratory cancer among chromate workers. *J Occup Med*, 16: 523–526. PMID:4843401

EVM Expert Group on Vitamins and Minerals Secretariat (2002). *Review of chromium.* UK: EVM/99/26. REVISEDAUG2002, 25. 2002.

Faux SP, Gao M, Chipman JK, Levy LS (1992). Production of 8-hydroxydeoxyguanosine in isolated DNA by chromium(VI) and chromium(V). *Carcinogenesis*, 13: 1667–1669. doi:10.1093/carcin/13.9.1667 PMID:1327573

Furst A, Schlauder M, Sasmore DP (1976). Tumorigenic activity of lead chromate. *Cancer Res*, 36: 1779–1783. PMID:1268834

Gambelunghe A, Piccinini R, Ambrogi M *et al.* (2003). Primary DNA damage in chrome-plating workers. *Toxicology*, 188: 187–195. PMID:12767690

Gao M, Binks SP, Chipman JK *et al.* (1992). Induction of DNA strand breaks in peripheral lymphocytes by soluble chromium compounds. *Hum Exp Toxicol*, 11: 77–82. doi:10.1177/096032719201100203 PMID:1349223

Gianello G, Masci O, Carelli G *et al.* (1998). Occupational exposure to chromium – an assessment of environmental pollution levels and biological monitoring of

exposed workers. *Ind Health*, 36: 74–77. doi:10.2486/indhealth.36.74 PMID:9473863

Glaser U, Hochrainer D, Klöppel H, Oldiges H (1986). Carcinogenicity of sodium dichromate and chromium (VI/III) oxide aerosols inhaled by male Wistar rats. *Toxicology*, 42: 219–232. doi:10.1016/0300-483X(86)90011-9 PMID:3798470

Guertin J, Jacobs JA, Avakian CP (2004). *Chromium (VI) Handbook*. Boca Raton, FL: CRC Press, pp. 800.

Hall R, Rhodes D, Page E (2005). *Evaluation of worker exposures during the manufacturing of high quality corrosive resistant stainless steel products and fabricated piping systems*. American Industrial Hygiene Conference and Expo, Anaheim, CA: May 21–26, 2005. Fairfax, VA: American Industrial Hygiene Association, pp. 59.

Hassoun EA & Stohs SJ (1995). Chromium-induced production of reactive oxygen species, DNA single-strand breaks, nitric oxide production, and lactate dehydrogenase leakage in J774A.1 cell cultures. *J Biochem Toxicol*, 10: 315–321. doi:10.1002/jbt.2570100606 PMID:8934634

Hueper WC (1961). Environmental carcinogenesis and cancers. *Cancer Res*, 21: 842–857. PMID:13716558

Hueper WC & Payne WW (1959). Experimental cancers in rats produced by chromium compounds and their significance to industry and public health. *Am Ind Hyg Assoc J*, 20: 274–280. PMID:13670103

Hueper WC & Payne WW (1962). Experimental studies in metal carcinogenesis. Chromium, nickel, iron, arsenic. *Arch Environ Health*, 5: 445–462. PMID:13955488

IARC (1973). Some inorganic and organometallic compounds. *IARC Monogr Eval Carcinog Risk Chem Man*, 2: 1–181.

IARC (1979). Chemicals and industrial processes associated with cancer in humans. IARC Monographs, volumes 1 to 20. *IARC Monogr Eval Carcinog Risk Chem Hum Suppl*, 1: 1–71. PMID:296141

IARC (1980). Some metals and metallic compounds. *IARC Monogr Eval Carcinog Risk Chem Hum*, 23: 1–415. PMID:6933135

IARC (1982). Chemicals, industrial processes and industries associated with cancer in humans (IARC Monographs, volumes 1 to 29). *IARC Monogr Eval Carcinog Risk Chem Hum Suppl*, 4: 1–292.

IARC (1987). Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 7: 1–440. PMID:3482203

IARC (1990). Chromium, nickel and welding. *IARC Monogr Eval Carcinog Risks Hum*, 49: 1–648. PMID:2232124

Kotaś J & Stasicka Z (2000). Chromium occurrence in the environment and methods of its speciation. *Environ Pollut*, 107: 263–283. doi:10.1016/S0269-7491(99)00168-2 PMID:15092973

Krystek P & Ritsema R (2007). Monitoring of chromium species and 11 selected metals in emission and immission of airborne environment. *Int J Mass Spectrom*, 265: 23–29. doi:10.1016/j.ijms.2007.05.003

Levy LS, Martin PA, Bidstrup PL (1986). Investigation of the potential carcinogenicity of a range of chromium containing materials on rat lung. *Br J Ind Med*, 43: 243–256. PMID:3964573

Levy LS & Venitt S (1986). Carcinogenicity and mutagenicity of chromium compounds: the association between bronchial metaplasia and neoplasia. *Carcinogenesis*, 7: 831–835. doi:10.1093/carcin/7.5.831 PMID:3698209

Lide DR, editor (2008). *CRC Handbook of Chemistry and Physics*, 88th ed. New York, NY: CRC Press, Taylor & Francis Group, pp. 4–50.

Luce D, Gérin M, Leclerc A *et al*. (1993). Sinonasal cancer and occupational exposure to formaldehyde and other substances. *Int J Cancer*, 53: 224–231. doi:10.1002/ijc.2910530209 PMID:8425759

Luippold RS, Mundt KA, Dell LD, Birk T (2005). Low-level hexavalent chromium exposure and rate of mortality among US chromate production employees. *J Occup Environ Med*, 47: 381–385. doi:10.1097/01.jom.0000158703.32263.0d PMID:15824629

Lurie P & Wolfe SM (2002). Continuing exposure to hexavalent chromium, a known lung carcinogen: an analysis of OSHA compliance inspections, 1990–2000. *Am J Ind Med*, 42: 378–383. doi:10.1002/ajim.10128 PMID:12382250

Maltoni C (1974). Occupational carcinogenesis. *Excerpta med int Congr Ser*, 322: 19C.bib_lpa$-Char>26C.bib_lpa$-Char.

Maltoni C (1976). Occupational carcinogenesis. Predictive value of carcinogenesis bioassays. *Ann N Y Acad Sci*, 271: 1 Neoplasia in431–443. doi:10.1111/j.1749-6632.1976.tb23144.x PMID:1069535

Maltoni C, Morisi L, Chieco P (1982). Experimental approach to the assessment of the carcinogenic risk of industrial inorganic pigments *Adv mod environ Toxicol*, 2: 7792.

Mukherjee AB (1998). Chromium in the environment of Finland. *Sci Total Environ*, 217: 9–19. doi:10.1016/S0048-9697(98)00163-6 PMID:9695169

Nettesheim P, Hanna MG Jr, Doherty DG *et al*. (1971). Effect of calcium chromate dust, influenza virus, and 100 R whole-body x radiation on lung tumor incidence in mice. *J Natl Cancer Inst*, 47: 1129–1144. PMID:10787327

Newman D (1890). A case of adeno-carcinoma of the left inferior turbinated body, and perforation of the nasal septum, in the person of a worker in chrome pigments. *Glasg Med J*, 33: 469–470.

NTP (2005). NTP 11th Report on Carcinogens *Rep Carcinog*, 11: 1–A32. PMID:19826456

NTP (2008). NTP Toxicology and Carcinogenesis Studies of Sodium Dichromate Dihydrate (CAS No. 7789–12–0) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). *Natl Toxicol Program Tech Rep Ser*, 546: 1–192. PMID:18716633

OHCOW (2005). *Hexavalent Chromium*. Ontario, Canada: Occupational Health Clinics for Ontario Workers Inc.

OSHA; Occupational Safety and Health Administration. Department of Labor (2006). Occupational exposure to hexavalent chromium. Final rule. *Fed Regist*, 71: 10099–10385. PMID:16528853

Parkin D, Whelan S, Ferlay J *et al.*, editors (1997). *Cancer Incidence in Five Continents. volume VII.* Lyon: IARC Press.

Paschin YV, Zacepilova TA, Kozachenko VI (1982). Induction of dominant lethal mutations in male mice by potassium dichromate. *Mutat Res*, 103: 345–347. doi:10.1016/0165-7992(82)90065-3 PMID:7087995

Paustenbach DJ, Finley BL, Mowat FS, Kerger BD (2003). Human health risk and exposure assessment of chromium (VI) in tap water. *J Toxicol Environ Health, Part A*, 66: 1295–1339. doi:10.1080/15287390306388 PMID:12851114

Payne WW (1960). Production of cancers in mice and rats by chromium compounds. *AMA Arch Ind Health*, 21: 530–535. PMID:14431169

Pfeil E (1935). Lung tumors as occupational disease in chromate plants (Ger.). *Dtsch Med Wochenschr*, 61: 1197–1200. doi:10.1055/s-0028-1122461

Proctor DM, Otani JM, Finley BL *et al.* (2002). Is hexavalent chromium carcinogenic via ingestion? A weight-of-evidence review. *J Toxicol Environ Health A*, 65: 701–746. doi:10.1080/00984100290071018 PMID:12028825

Proctor DM, Panko JP, Liebig EW *et al.* (2003). Workplace airborne hexavalent chromium concentrations for the Painesville, Ohio, chromate production plant (1943–1971). *Appl Occup Environ Hyg*, 18: 430–449. doi:10.1080/10473220301421 PMID:12746066

Quievryn G, Messer J, Zhitkovich A (2002). Carcinogenic chromium(VI) induces cross-linking of vitamin C to DNA in vitro and in human lung A549 cells. *Biochemistry*, 41: 3156–3167. doi:10.1021/bi011942z PMID:11863455

Quievryn G, Peterson E, Messer J, Zhitkovich A (2003). Genotoxicity and mutagenicity of chromium(VI)/ascorbate-generated DNA adducts in human and bacterial cells. *Biochemistry*, 42: 1062–1070. doi:10.1021/bi0271547 PMID:12549927

Reinds GJ, Groenenberg JE, de Vries W (2006). *Critical loads of copper, nickel zinc, arsenic, chromium and selenium for terrestrial ecosystems at a European scale: A preliminary assessment (Alterra Report 1355).* Wageningen, pp. 45.

Reynolds M, Stoddard L, Bespalov I, Zhitkovich A (2007). Ascorbate acts as a highly potent inducer of chromate mutagenesis and clastogenesis: linkage to DNA breaks in G2 phase by mismatch repair. *Nucleic Acids Res*, 35: 465–476. doi:10.1093/nar/gkl1069 PMID:17169990

Roe FJ & Carter RL (1969). Chromium carcinogenesis: calcium chromate as a potent carcinogen for the subcutaneous tissues of the rat. *Br J Cancer*, 23: 172–176. PMID:5768433

Rowbotham AL, Levy LS, Shuker LK (2000). Chromium in the environment: an evaluation of exposure of the UK general population and possible adverse health effects. *J Toxicol Environ Health B Crit Rev*, 3: 145–178. doi:10.1080/10937400050045255 PMID:10911983

Salnikow K & Zhitkovich A (2008). Genetic and epigenetic mechanisms in metal carcinogenesis and cocarcinogenesis: nickel, arsenic, and chromium. *Chem Res Toxicol*, 21: 28–44. doi:10.1021/tx700198a PMID:17970581

Sedman RM, Beaumont J, McDonald TA *et al.* (2006). Review of the evidence regarding the carcinogenicity of hexavalent chromium in drinking water. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev*, 24: 155–182. PMID:16690539

Shi X, Mao Y, Knapton AD *et al.* (1994). Reaction of Cr(VI) with ascorbate and hydrogen peroxide generates hydroxyl radicals and causes DNA damage: role of a Cr(IV)-mediated Fenton-like reaction. *Carcinogenesis*, 15: 2475–2478. doi:10.1093/carcin/15.11.2475 PMID:7955094

Sorahan T, Burges DC, Waterhouse JA (1987). A mortality study of nickel/chromium platers. *Br J Ind Med*, 44: 250–258. PMID:3567099

Standeven AM, Wetterhahn KE, Kato R (1992). Ascorbate is the principal reductant of chromium(VI) in rat lung ultrafiltrates and cytosols, and mediates chromium-DNA binding in vitro. *Carcinogenesis*, 13: 1319–1324. doi:10.1093/carcin/13.8.1319 PMID:1499083

Stearns DM & Wetterhahn KE (1994). Reaction of chromium(VI) with ascorbate produces chromium(V), chromium(IV), and carbon-based radicals. *Chem Res Toxicol*, 7: 219–230. doi:10.1021/tx00038a016 PMID:8199312

Steinhoff D, Gad SC, Hatfield GK, Mohr U (1986). Carcinogenicity study with sodium dichromate in rats. *Exp Pathol*, 30: 129–141. PMID:3792485

Takahashi Y, Kondo K, Hirose T *et al.* (2005). Microsatellite instability and protein expression of the DNA mismatch repair gene, hMLH1, of lung cancer in chromate-exposed workers. *Mol Carcinog*, 42: 150–158. doi:10.1002/mc.20073 PMID:15605365

Teleky L (1936). Cancer in chromium workers (Ger.). *Dtsch Med Wochenschr*, 62: 1353 doi:10.1055/s-0028-1141271

Teschke K, Ahrens W, Andersen A *et al.* (1999). Occupational exposure to chemical and biological agents in the nonproduction departments of pulp, paper, and paper product mills: an international study. *Am Ind Hyg Assoc J*, 60: 73–83. PMID:10028618

Uddin AN, Burns FJ, Rossman TG *et al.* (2007). Dietary chromium and nickel enhance UV-carcinogenesis

in skin of hairless mice. *Toxicol Appl Pharmacol*, 221: 329–338. doi:10.1016/j.taap.2007.03.030 PMID:17499830

Vaglenov A, Nosko M, Georgieva R *et al.* (1999). Genotoxicity and radioresistance in electroplating workers exposed to chromium. *Mutat Res*, 446: 23–34. PMID:10613183

Wetterhahn KE & Hamilton JW (1989). Molecular basis of hexavalent chromium carcinogenicity: effect on gene expression. *Sci Total Environ*, 86: 113–129. doi:10.1016/0048-9697(89)90199-X PMID:2602931

Wetterhahn KE, Hamilton JW, Aiyar J *et al.* (1989). Mechanism of chromium(VI) carcinogenesis. Reactive intermediates and effect on gene expression. *Biol Trace Elem Res*, 21: 405–411. doi:10.1007/BF02917282 PMID:2484620

Wu FY, Wu WY, Kuo HW *et al.* (2001). Effect of genotoxic exposure to chromium among electroplating workers in Taiwan. *Sci Total Environ*, 279: 21–28. doi:10.1016/S0048-9697(01)00685-4 PMID:11712598

Xie H, Holmes AL, Wise SS *et al.* (2007). Neoplastic transformation of human bronchial cells by lead chromate particles. *Am J Respir Cell Mol Biol*, 37: 544–552. doi:10.1165/rcmb.2007-0058OC PMID:17585109

Yao H, Guo L, Jiang BH *et al.* (2008). Oxidative stress and chromium(VI) carcinogenesis. *J Environ Pathol Toxicol Oncol*, 27: 77–88. PMID:18540844

Yuann JM, Liu KJ, Hamilton JW, Wetterhahn KE (1999). In vivo effects of ascorbate and glutathione on the uptake of chromium, formation of chromium(V), chromium-DNA binding and 8-hydroxy-2′-deoxyguanosine in liver and kidney of osteogenic disorder shionogi rats following treatment with chromium(VI). *Carcinogenesis*, 20: 1267–1275. doi:10.1093/carcin/20.7.1267 PMID:10383900

Zhang JD & Li XL (1987). Chromium pollution of soil and water in Jinzhou *Zhonghua Yu Fang Yi Xue Za Zhi*, *Chinese Journal of Preventive Medicine*,)21: 262–264. PMID:3443034

Zhitkovich A (2005). Importance of chromium-DNA adducts in mutagenicity and toxicity of chromium(VI). *Chem Res Toxicol*, 18: 3–11. doi:10.1021/tx049774+ PMID:15651842

Zhitkovich A, Song Y, Quievryn G, Voitkun V (2001). Non-oxidative mechanisms are responsible for the induction of mutagenesis by reduction of Cr(VI) with cysteine: role of ternary DNA adducts in Cr(III)-dependent mutagenesis. *Biochemistry*, 40: 549–560. doi:10.1021/bi0015459 PMID:11148050

NICKEL AND NICKEL COMPOUNDS

Nickel and nickel compounds were considered by previous IARC Working Groups in 1972, 1975, 1979, 1982, 1987, and 1989 (IARC, 1973, 1976, 1979, 1982, 1987, 1990). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agents

Synonyms, trade names, and molecular formulae for nickel, nickel alloys, and selected nickel compounds are presented in Table 1.1. This list is not exhaustive, nor does it necessarily reflect the commercial importance of the various nickel-containing substances, but it is indicative of the range of nickel alloys and compounds available, including some compounds that are important commercially, and those that have been tested in biological systems. Several intermediary compounds occur in refineries that cannot be characterized, and are thus not listed.

1.2 Chemical and physical properties of the agents

Nickel (atomic number, 28; atomic weight, 58.69) is a metal, which belongs to group VIIIB of the periodic table. The most important oxidation state of nickel is +2, although the +3 and +4 oxidation states are also known (Tundermann *et al.*, 2005). Nickel resembles iron, cobalt, and copper in its chemical properties. However, unlike cobalt and iron, it is normally only stable in aqueous solution in the + 2 oxidation state (Kerfoot, 2002). Selected chemical and physical properties for nickel and nickel compounds, including solubility data, were presented in the previous *IARC Monograph* (IARC, 1990), and have been reported elsewhere (ATSDR, 2005).

1.3 Use of the agents

The chemical properties of nickel (i.e. hardness, high melting point, ductility, malleability, somewhat ferromagnetic, fair conductor of heat and electricity) make it suitable to be combined with other elements to form many alloys (NTP, 2000; Tundermann *et al.*, 2005). It imparts such desirable properties as corrosion resistance, heat resistance, hardness, and strength.

Nickel salts are used in electroplating, ceramics, pigments, and as intermediates (e.g. catalysts, formation of other nickel compounds). Sinter nickel oxide is used in nickel catalysts in the ceramics industry, in the manufacture of alloy steel and stainless steel, in the manufacture of nickel salts for specialty ceramics, and in the manufacture of nickel–cadmium (Ni–Cd) batteries, and nickel–metal-hydride batteries. Nickel sulfide is used as a catalyst in

Table 1.1 Chemical names (CAS names are given in italics), synonyms, and molecular formulae or compositions of nickel, nickel alloys and selected nickel compounds

Chemical name	CAS Reg. No.	Synonyms	Formula
Metallic nickel and nickel alloys			
Nickel	7440-02-0	C.I. 77775; Nickel element	Ni
Ferronickel	11133-76-9	*Iron alloy (base), Fe, Ni*; nickel alloy (nonbase) Fe, Ni	Fe, Ni
Nickel aluminium alloys	61431-86-5 37187-84-1	*Raney nickel*; Raney alloy	NiAl
Nickel oxides and hydroxides			
Nickel hydroxide (amorphous)	12054-48-7 (11113-74-9)	Nickel dihydroxide; nickel (II) hydroxide; nickel (2+) hydroxide; *nickel hydroxide (Ni(OH)2)*; nickelous hydroxide	$Ni(OH)_2$
Nickel monoxide	1313-99-1 11099-02-8 34492-97-2	Black nickel oxide[a]; green nickel oxide; mononickel oxide; nickel monooxide; nickelous oxide; *nickel oxide (NiO)*; nickel (II) oxide; nickel (2+) oxide *Bunsenite (NiO)*	NiO
Nickel trioxide	1314-06-3	Black nickel oxide*d*; dinickel trioxide; nickelic oxide; nickel oxide; nickel (III) oxide; *nickel oxide (Ni_2O_3)*; nickel peroxide; nickel sesquioxide	Ni_2O_3
Nickel sulfides			
Nickel disulfide	12035-51-7 12035-50-6	*Nickel sulfide (NiS_2)* *Vaesite (NiS_2)*	NiS_2
Nickel sulfide (amorphous)	16812-54-7 (11113-75-0) 1314-04-1 (61026-96-8)	Mononickel monosulfide; nickel mono-sulfide; nickel monosulfide (NiS); nickelous sulfide; nickel (II) sulfide; nickel (2+) sulfide; *Nickel sulfide (NiS)* *Millerite (NiS)*	NiS
Nickel subsulfide	12035-72-2 12035-71-1	Nickel sesquisulfide; nickel subsulfide (Ni_3S_2); *nickel sulfide (Ni_3S_2)*; trinickel disulfide *Heazlewoodite (Ni_3S_2)*; Khizlevudite	Ni_3S_2
Pentlandite	53809-86-2 12174-14-0	Pentlandite ($Fe_9Ni_9S_{16}$) Pentlandite	Fe9Ni9S16 $(Fe_{0.4-0.6}Ni_{0.4-0.6})_9S_8$

Table 1.1 (continued)

Chemical name	CAS Reg. No.	Synonyms	Formula
Nickel salts			
Nickel carbonate	3333-67-3	*Carbonic acid, nickel (2+) salt (1:1)*; nickel carbonate (1:1); nickel (II) carbonate; nickel (2+) carbonate; nickel carbonate ($NiCO_3$); nickel (2+) carbonate ($NiCO_3$); nickel monocarbonate; nickelous carbonate	$NiCO_3$
Basic nickel carbonates	12607-70-4	Carbonic acid, nickel salt, basic; nickel carbonate hydroxide ($Ni_3(CO_3)(OH)_4$); *nickel, (carbonato(2-)) tetrahydroxytri-*	$NiCO_3.2Ni(OH)_2$
	12122-15-5	*Nickel bis(carbonato(2-)) hexahydroxypenta-*; nickel hydroxycarbonate	$2NiCO_3.3Ni(OH)_2$
Nickel acetate	373-02-4	*Acetic acid, nickel (2+) salt*; nickel (II) acetate; nickel (2+) acetate; nickel diacetate; nickelous acetate	$Ni(OCOCH_3)_2$
Nickel acetate tetrahydrate	6018-89-9	*Acetic acid, nickel (+2) salt, tetrahydrate*	$Ni(OCOCH_3)_2.4H_2O$
Nickel ammonium sulfates	15-699-18-0	Ammonium nickel sulfate ($(NH_4)_2Ni(SO_4)_2$); nickel ammonium sulfate ($Ni(NH_4)_2(SO_4)_2$); *sulfuric acid, ammonium nickel (2+) salt (2:2:1)*	$Ni(NH_4)_2(SO_4)_2$
Nickel ammonium sulfate hexahydrate	25749-08-0	Ammonium nickel sulfate ($(NH_4)_2Ni_2(SO_4)_3$); *sulfuric acid, ammonium nickel (2+) salt (3:2:2)*	$Ni_2(NH_4)_2(SO_4)_3$
	7785-20-8	Ammonium nickel (2+) sulfate hexahydrate; ammonium nickel sulfate ($(NH_4)_2Ni(SO_4)_2$); diammonium nickel disulfate hexahydrate; diammonium nickel (2+) disulfate hexahydrate; nickel ammonium sulfate ($Ni(NH_4)_2(SO_4)_2$) hexahydrate; nickel diammonium disulfate hexahydrate; *sulfuric acid, ammonium nickel (2+) salt (2:2:1), hexahydrate*	$Ni(NH_4)_2(SO_4)_2.6H_2O$
Nickel chromate	14721-18-7	*Chromium nickel oxide ($NiCrO_4$)*; nickel chromate ($NiCrO_4$); nickel chromium oxide ($NiCrO_4$)	$NiCrO_4$
Nickel chloride	7718-54-9	Nickel (II) chloride; nickel (2+) chloride; *nickel chloride ($NiCl_2$)*; nickel dichloride; nickel dichloride ($NiCl_2$); nickelous cholride	$NiCl_2$
Nickel chloride hexahydrate	7791-20-0	*Nickel chloride (NiCl2) hexahydrate*	$NiCl_2.6H_2O$
Nickel nitrate hexahydrate	13478-00-7	Nickel (2+) bis(nitrate)hexahydrate; nickel dinitrate hexahydrate; nickel (II) nitrate hexahydrate; nickel nitrate (Ni(NO3)2) hexahydrate; nickelous nitrate hexahydrate; *nitric acid, nickel (2+) salt, hexahydrate*	$Ni(NO_3)_2.6H_2O$
Nickel sulfate	7786-81-4	Nickel monosulfate; nickelous sulfate; nickel sulfate (1:1); nickel (II) sulfate; nickel (2+) sulfate; nickel (2+) sulfate (1:1); nickel sulfate ($NiSO_4$); *sulfuric acid, nickel (2+) salt (1:1)*	$NiSO_4$
Nickel sulfate hexahydrate	10101-97-0	*Sulfuric acid, nickel (2+) salt (1:1), hexahydrate*	$NiSO_4.6H_2O$
Nickel sulfate heptahydrate	10101-98-1	*Sulfuric acid, nickel (2+) salt (1:1), heptahydrate*	$NiSO_4.7H_20$

Table 1.1 (continued)

Chemical name	CAS Reg. No.	Synonyms	Formula
Other nickel compounds			
Nickel carbonyl	13463-39-3	*Nickel carbonyl (Ni(CO)$_4$), (T-4)-*; nickel tetracarbonyl; tetracarbonylnickel; tetracarbonylnickel (0)	$Ni(CO)_4$
Nickel antimonide	12035-52-8	*Antimony compound with nickel (1:1)*; nickel antimonide (NiSb); nickel compound with antimony (1:1); nickel monoantimonide	NiSb
	12125-61-0	*Breithauptite (SbNi)*	
Nickel arsenides	27016-75-7	*Nickel arsenide (NiAs)*	NiAs
	1303-13-5	Nickeline; *nickeline (NiAs)*; niccolite	NiAs
	12256-33-6	*Nickel arsenide ($Ni_{11}As_8$)*; nickel arsenide tetragonal	$Ni_{11}As_8$
	12044-65-4	*Maucherite ($Ni_{11}As_8$)*; Placodine; Temiskamite	$Ni_{11}As_8$
	12255-80-0	*Nickel arsenide (Ni_5As_2)*; nickel arsenide hexagonal	Ni_5As_2
Nickel selenide	1314-05-2	Nickel monoselenide; *nickel selenide (NiSe)*	NiSe
	12201-85-3	Maekinenite; *Makinenite (NiSe)*	
Nickel subselenide	12137-13-2	*Nickel selenide (Ni_3Se_2)*	Ni_3Se_2
Nickel sulfarsenide	12255-10-6	*Nickel arsenide sulfide (NiAsS)*	NiAsS
	12255-11-7	*Gersdorffite (NiAsS)*	
Nickel telluride	12142-88-0	Nickel monotelluride; *nickel telluride (NiTe)*	NiTe
	24270-51-7	*Imgreite (NiTe)*	
Nickel titanate	12035-39-1	Nickel titanate(IV); nickel titanate (Ni-TiO3); *nickel titanium oxide (NiTiO3)*; nickel titanium trioxide	$NiTiO_3$
Chrome iron nickel black spinel	71631-15-7	CI: 77 504; *CI Pigment Black 30*; nickel iron chromite black spinel	$(Ni,Fe)(CrFe)_2O_4$ NS
Nickel ferrite brown spinel	68187-10-0	*CI Pigment Brown 34*	$NiFe_2O_4$
Nickelocene	1271-28-9	Bis(η5-2,4-cyclopentadien-1-yl)nickel; di-π-cyclopentadienylnickel; dicyclopentadienyl-nickel; bis(η5-2,4-cyclopentadien-1-yl)-nickel	π-(C5H5)2Ni

[a] In commercial usage, 'black nickel oxide' usually refers to the low-temperature crystalline form of nickel monoxide, but nickel trioxide (Ni_2O_3), an unstable oxide of nickel, may also be called 'black nickel oxide'.

the petrochemical industry or as an intermediate in the metallurgical industry.

According to the US Geological Survey, world use of primary nickel in 2006 was 1.40 million tonnes, a 12% increase over 2005. Stainless steel manufacture accounted for more than 60% of primary nickel consumption in 2006 (USGS, 2008). Of the 231000 tonnes of primary nickel consumed in the USA in 2007, approximately 52% was used in stainless and alloy steel production, 34% in non-ferrous alloys and superalloys, 10% in electroplating, and 4% in other uses. End uses of nickel in the USA in 2007 were as follows: transportation, 30%; chemical industry, 15%; electrical equipment, 10%; construction, 9%; fabricated metal products, 8%; household appliances, 8%; petroleum industry, 7%; machinery, 6%; and others, 7% (Kuck, 2008).

1.3.1 Metallic nickel and nickel alloys

Pure nickel metal is used to prepare nickel alloys (including steels). It is used as such for plating, electroforming, coinage, electrical components, tanks, catalysts, battery plates, sintered components, magnets, and welding rods. Ferronickel is used to prepare steels. Stainless and heat-resistant steels accounted for 93% of its end-use in 1986. Nickel-containing steels with low nickel content (< 5%) are used in construction and tool fabrication. Stainless steels are used in general engineering equipment, chemical equipment, domestic applications, hospital equipment, food processing, architectural panels and fasteners, pollution-control equipment, cryogenic uses, automotive parts, and engine components (IARC, 1990).

Nickel alloys are often divided into categories depending on the primary metal with which they are alloyed (e.g. iron, copper, molybdenum, chromium) and their nickel content. Nickel is alloyed with iron to produce alloy steels (containing 0.3–5% nickel), stainless steels (containing as much as 25–30% nickel, although 8–10% nickel is more typical), and cast irons. Nickel–copper alloys (e.g. Monel alloys) are used for coinage (25% nickel, 75% copper), industrial plumbing (e.g. piping and valves), marine equipment, petrochemical equipment, heat exchangers, condenser tubes, pumps, electrodes for welding, architectural trim, thermocouples, desalination plants, ship propellers, etc. Nickel–chromium alloys (e.g. Nichrome) are used in many applications that require resistance to high temperatures such as heating elements, furnaces, jet engine parts, and reaction vessels. Molybdenum-containing nickel alloys and nickel–iron–chromium alloys (e.g. Inconel) provide strength and corrosion resistance over a wide temperature range, and are used in nuclear and fossil-fuel steam generators, food-processing equipment, and chemical-processing and heat-treating equipment. Hastelloy alloys (which contain nickel, chromium, iron, and molybdenum) provide oxidation and corrosion resistance for use with acids and salts. Nickel-based super-alloys provide high-temperature strength and creep, and stress resistance for use in gas-turbine engines (ATSDR, 2005).

Other groups of nickel alloys are used according to their specific properties for acid-resistant equipment, heating elements for furnaces, low-expansion alloys, cryogenic uses, storage of liquefied gases, high-magnetic-permeability alloys, and surgical implant prostheses.

1.3.2 Nickel oxides and hydroxides

The nickel oxide sinters are used in the manufacture of alloy steels and stainless steels.

Green nickel oxide is a finely divided, relatively pure form of nickel monoxide, produced by firing a mixture of nickel powder and water in air at 1000 °C (IARC, 1990). It is used to manufacture nickel catalysts and specialty ceramics (for porcelain enamelling of steel; in the manufacture of magnetic nickel-zinc ferrites used in electric motors, antennas and television tube yokes; and

as a colourant in glass and ceramic stains used in ceramic tiles, dishes, pottery, and sanitary ware).

Black nickel oxide is a finely divided, pure nickel monoxide, produced by calcination of nickel hydroxycarbonate or nickel nitrate at 600 °C; nickel trioxide (Ni_2O_3), an unstable oxide of nickel, may also be called 'black nickel oxide' (IARC, 1990). Black nickel oxide is used in the manufacture of nickel salts, specialty ceramics, and nickel catalysts (e.g. to enhance the activity of three-way catalysts containing rhodium, platinum, and palladium used in automobile exhaust control).

Nickel hydroxide is used as a catalyst intermediate, and in the manufacture of Ni–Cd batteries (Antonsen & Meshri, 2005).

1.3.3 Nickel sulfides

Nickel sulfide is used as a catalyst in petrochemical hydrogenation when high concentrations of sulfur are present in the distillates. The major use of nickel monosulfide is as an intermediate in the hydrometallurgical processing of silicate-oxide nickel ores (IARC, 1990). Nickel subsulfide is used as an intermediate in the primary nickel industry (ATSDR, 2005).

1.3.4 Nickel salts

Nickel acetate is used in electroplating, as an intermediate (e.g. as catalysts and in the formation of other nickel compounds), as a dye mordant, and as a sealer for anodized aluminium.

Nickel carbonate is used in the manufacture of nickel catalysts, pigments, and other nickel compounds (e.g. nickel oxide, nickel powder); in the preparation of coloured glass; and, as a neutralizing compound in nickel-electroplating solutions.

Nickel ammonium sulfate is used as a dye mordant, in metal-finishing compositions, and as an electrolyte for electroplating.

Nickel chloride is used as an intermediate in the manufacture of nickel catalysts, and to absorb ammonia in industrial gas masks.

Nickel nitrate hexahydrate is used as an intermediate in the manufacture of nickel catalysts and Ni–Cd batteries.

Nickel sulfate hexahydrate is used in nickel electroplating and nickel electrorefining, in 'electroless' nickel plating, and as an intermediate (in the manufacture of other nickel chemicals and catalysts) (Antonsen & Meshri, 2005).

1.3.5 Other nickel compounds

The primary use for nickel carbonyl is as an intermediate (in the production of highly pure nickel), as a catalyst in chemical synthesis, as a reactant in carbonylation reactions, in the vapour-plating of nickel, and in the fabrication of nickel and nickel alloy components and shapes.

Nickelocene is used as a catalyst and complexing agent, and nickel titanate is used as a pigment (Antonsen & Meshri, 2005).

No information was available to the Working Group on the use of nickel selenides or potassium nickelocyanate.

1.4 Environmental occurrence

Nickel and its compounds are naturally present in the earth's crust, and are emitted to the atmosphere via natural sources (such as windblown dust, volcanic eruptions, vegetation forest fires, and meteoric dust) as well as from anthropogenic activities (e.g. mining, smelting, refining, manufacture of stainless steel and other nickel-containing alloys, fossil fuel combustion, and waste incineration). Estimates for the emission of nickel into the atmosphere from natural sources range from 8.5 million kg/year in the 1980s to 30 million kg/year in the early 1990s (ATSDR, 2005). The general population is exposed to low levels of nickel in ambient air, water, food, and through tobacco consumption.

1.4.1 Natural occurrence

Nickel is widely distributed in nature and is found in animals, plants, and soil (EVM, 2002). It is the 24th most abundant element, forming about 0.008% of the earth's crust (0.01% in igneous rocks). The concentration of nickel in soil is approximately 79 ppm, with a range of 4–80 ppm (EVM, 2002; ATSDR, 2005).

1.4.2 Air

Nickel is emitted to the atmosphere from both natural and anthropogenic sources. It has been estimated that approximately 30000 tonnes of nickel may be emitted per year to the atmosphere from natural sources. The anthropogenic emission rate is estimated to be between 1.4–1.8 times higher than the natural emission rate.

The two main natural sources are volcanoes and windblown dust from rocks and soil, estimated to respectively contribute 14000 tonnes/year and 11000 tonnes/year (NTP, 2000; Barbante *et al.*, 2002). Other relatively minor sources include: wild forest fires (2300 tonnes/year), sea salt spray (1300 tonnes/year), continental particulates (510 tonnes/year), marine (120 tonnes/year), and continental volatiles (100 tonnes/year) (Barbante *et al.*, 2002).

Anthropogenic activities release nickel to the atmosphere, mainly in the form of aerosols (ATSDR, 2005). Fossil fuel combustion is reported to be the major contributor of atmospheric nickel in Europe and the world, accounting for 62% of anthropogenic emissions in the 1980s (Barbante *et al.*, 2002; ATSDR, 2005). In 1999, an estimated 570000 tons of nickel were released from the combustion of fossil fuels worldwide (Rydh & Svärd, 2003). Of this, 326 tons were released from electric utilities (Leikauf, 2002). Of the other anthropogenic sources, nickel metal and refining accounted for 17% of total emissions, municipal incineration 12%, steel production 3%, other nickel-containing alloy production 2%, and coal combustion 2% (ATSDR, 2005).

Atmospheric nickel concentrations are higher in rural and urban air (concentration range: 5–35 ng/m^3) than in remote areas (concentration range: 1–3 ng/m^3) (WHO, 2007).

1.4.3 Water

Particulate nickel enters the aquatic environment from a variety of natural and anthropogenic sources. Natural sources include the weathering and dissolution of nickel-containing rocks and soil, disturbed soil, and atmospheric deposition. Anthropogenic sources include: industrial processes (e.g. mining and smelting operations), industrial waste water and effluent (e.g. tailings piles run-off), domestic waste water, and landfill leachate (NTP, 2000; ATSDR, 2005; WHO, 2007). Several factors influence the concentration of nickel in groundwater and surface water including: soil use, pH, and depth of sampling (WHO, 2007). Most nickel compounds are relatively water soluble at low pH (i.e. pH < 6.5). As a result, acid rain tends to increase the mobility of nickel in soil, which, in turn, has a corresponding impact on nickel concentrations in groundwater (NTP, 2000; WHO, 2007).

Based on measurement data from the 1980s, the following average nickel concentrations have been reported for groundwater, seawater and surface water, respectively: < 20 µg/L, 0.1–0.5 µg/L, and 15–20 µg/L (NTP, 2000; ATSDR, 2005). Nickel concentrations as high as 980 µg/L have been measured in groundwater with pH < 6.2 (WHO, 2007). Levels of dissolved nickel ranging from < 1–87 µg/L have been reported in urban storm run-off water samples (ATSDR, 2005).

Nickel concentrations in the range of 6–700 pg/g have been measured in high-altitude snow and ice near the summit of Mont Blanc on the French-Italian border. Seasonal variations were observed, with higher concentrations in the summer layers than in the winter layers.

Nickel levels appeared to be more associated with anthropogenic inputs (e.g. oil combustion from power generation, automobile and truck traffic) than with natural sources, such as rock and soil dust (Barbante *et al.*, 2002).

1.4.4 Soil and sediments

Natural and anthropogenic sources (e.g. mining and smelting, coal fly ash, bottom ash, metal manufacturing waste, commercial waste, atmospheric fall-out and deposition, urban refuse, and sewage sludge) contribute to the levels of nickel found in soil and sediments (NTP, 2000; ATSDR, 2005). Of the nickel emitted to the environment, the largest releases are to the soil. In 2002, estimated releases of nickel and nickel compounds from manufacturing and processing facilities (required to report to the US Toxic Release Inventory Program) were approximately 5530 and 14800 metric tonnes, respectively—accounting for 82% and 87% of estimated total nickel releases to the environment (ATSDR, 2005).

In a study of urban soil quality, a harmonized sampling regime was used to compare concentrations of nickel in six European cities differing markedly in their climate and industrial history. The sites were as far as possible from current point sources of pollution, such as industrial emissions, but all were bordered by major roads, and are thus likely to have been affected by vehicle emissions. To assess the vertical distribution of soil parameters, two depths were sampled at each point: a surface sample at 0–10 cm and a subsurface sample at 10–20 cm. The surface sample mean nickel concentration was in the range of 11–207 mg /kg, and the corresponding mean concentration in the subsurface sample, 10–210 mg/kg (Madrid *et al.*, 2006).

1.5 Human exposure

1.5.1 Exposure of the general population

Ingestion of nickel in food, and to a lesser degree in drinking-water, is the primary route of exposure for the non-smoking general population. Exposure may also occur via inhalation of ambient air and percutaneous absorption (NTP, 2000; ATSDR, 2005; WHO, 2007). The daily intake of nickel from food and beverages varies by foodstuff, by country, by age, and by gender (EVM, 2002; ATSDR, 2005). Data from a study in the USA give estimates of daily dietary intakes in the range of 101–162 µg/day for adults, 136–140 µg/day for males, and 107–109 µg/day for females. Estimates for pregnant and lactating women are higher with average daily intakes of 121 µg/day and 162 µg/day, respectively (ATSDR, 2005). Based on the concordance between different studies of dietary intake, diet is reported to contribute less than 0.2 mg/day (WHO, 2007).

Inhalation of nickel from ambient air is generally a minor route of exposure for the general population. The following daily intakes of nickel have been estimated: less than 0.05 µg/day in the USA; 0.42 µg/day (mean ambient concentration) and 15 µg/day (highest ambient concentration) in the Sudbury basin region in Ontario, Canada; and, 122 µg/day (based on the highest ambient reported nickel concentration) in the Copper Cliff region of Ontario, Canada. These estimates are based on a breathing rate of 20 m^3/day, and nickel concentrations of 2.2 ng/m^3, 21 ng/m^3, 732 ng/m^3, and 6100 ng/m^3, respectively (ATSDR, 2005).

1.5.2 Occupational exposure

Nickel, in the form of various alloys and compounds, has been in widespread commercial use for over 100 years. Several million workers worldwide are exposed to airborne fumes, dusts and mists containing nickel and its compounds. Exposures by inhalation, ingestion or skin

contact occur in nickel-producing industries (e.g. mining, milling, smelting, and refining), as well as in nickel-using industries and operations (e.g. alloy and stainless steel manufacture; electroplating and electrowinning; welding, grinding and cutting). Insoluble nickel is the predominant exposure in nickel-producing industries, whereas soluble nickel is the predominant exposure in the nickel-using industries. Occupational exposure results in elevated levels of nickel in blood, urine and body tissues, with inhalation as the main route of uptake (IARC, 1990; NTP, 2000).

Estimates of the number of workers potentially exposed to nickel and nickel compounds have been developed by the National Institute of Occupational Safety and Health (NIOSH) in the USA and by CAREX (CARcinogen EXposure) in Europe. Based on the National Occupation Exposure Survey (NOES), conducted during 1981–1983, NIOSH estimated that 507681 workers, including 19673 female workers, were potentially exposed to 'Ni, Nickel-MF Unknown' (agent code: 50420) in the workplace (NIOSH, 1990). The following six industries accounted for nearly 60% of exposed workers: 'fabricated metal products' (n = 69984), 'special trade contractors' (n = 55178), 'machinery, except electrical' (n = 55064), 'transportation equipment' (n = 44838), 'primary metal industries' (n = 39467), and 'auto repair, services, and garages' (n = 27686). Based on occupational exposure to known and suspected carcinogens collected during 1990–1993, the CAREX database estimates that 547396 workers were exposed to nickel and nickel compounds in the European Union. Over 83% of these workers were employed in the 'manufacture of fabricated metal products, except machinery and equipment' (n = 195597), 'manufacture of machinery, except electrical' (n = 122985), 'manufacture of transport equipment' (n = 64720), 'non-ferrous base metal industries' (n = 32168), 'iron and steel basic industries' (n = 26504), and 'metal ore mining' (n = 16459). CAREX Canada (2011) estimates that approximately 50000 Canadians are exposed to nickel in the workplace (95% male). Exposed industries include: commercial/industrial machinery and equipment repair/maintenance; architectural, structural metals manufacturing; specialty trade contractors; boiler, tank and shipping container manufacturing; metal ore mining; motor vehicle parts manufacturing; machine shops, turned product, screw, nut and bolt manufacturing; coating, engraving, heat treating and allied activities; iron/steel mills and ferro-alloy manufacturing; non-ferrous metal production and processing.

Historically, metallic nickel exposures tended to be higher in nickel-producing industries than in the nickel-using industries, with estimates of historical mean levels of exposure to inhalable metallic nickel in the range of 0.01–6.0 mg/m^3 and 0.05–0.3 mg /m^3, respectively. However, data from the EU suggest that occasional higher exposures to inhalable metallic nickel may be present in certain industry sectors (Sivulka, 2005).

Data on early occupational exposures to nickel and nickel compounds were summarized in the previous *IARC Monograph* (IARC, 1990). Data from studies and reviews on nickel exposure published since the previous *IARC Monograph* are summarized below for both the nickel-producing and the nickel-using industries.

(a) *Studies of nickel-producing industries*

Ulrich *et al.* (1991) collected data on several indicators of nickel exposure (stationary and personal air sampling; urinary nickel excretion) among electrolytic nickel production workers in the Czech Republic (formerly, Czechoslovakia). Air samples (n = 52) were collected on membrane filters and analysed by electrothermal atomic absorption spectrometry. Urine samples (n = 140) were collected during the last 4 hours of workers' shifts, and the results were corrected to a standard density of 1.024. In a matched-pair analysis of air and urine samples collected from 18 electrolysis workers, the correlation coefficient

was 0.562; the mean concentration of nickel in urine was 53.3 µg/L (range, 1.73–98.55 µg/L), and the mean concentration in air was 0.187 mg/m^3 (range, 0.002–0.481 mg/m^3).

In a study conducted at a Finnish electrolytic nickel refinery, Kiilunen *et al.* (1997) collected data on nickel concentrations in air, blood, and urine. Stationary samples (n = 141) were collected from 50 locations in the refinery, including those areas where breathing zone samples were taken. Personal (i.e. 8-hour breathing zone) samples were collected over 4 successive work days (n = 157), from the shoulders when no respiratory protection was worn, inside the mask when protective equipment was worn, and inside the mask hanging on the shoulder of the worker when the mask was taken off. Historical occupational hygiene measurements were examined to assess past exposure. Spot urine samples (n = 154) were collected, pre- and post-shift, over 4 successive work days and 1 free day thereafter. Blood samples (n = 64) were collected at the beginning of the study and at the end of the last work shift. A total of 34 workers (of 100) volunteered to participate in the study. Urinary nickel results in the workers were compared with two non-exposed control groups (30 office workers from the refinery and 32 unexposed persons from the Helsinki area). For the stationary samples, nickel concentrations were reported by location as water-soluble nickel, acid-soluble nickel and total nickel (all in µg/m^3). Geometric mean nickel concentrations ranged from: 7.4 µg/m^3 ('other sites') to 451 µg/m^3 (in 'tank house 3′) for water-soluble nickel; 0.5 µg/m^3 ('other sites') to 4.6 µg/m^3 ('solution purification') for acid-soluble nickel; and, 7.6 µg/m^3 ('other sites') to 452 µg/m^3 (in 'tank house 3′). For the breathing zone samples, the range of geometric mean nickel concentrations was 0.2–3.2 µg/m^3 (inside the mask) and 0.6–63.2 µg/m^3 (no mask). Based on a review of historical stationary sampling data, average nickel concentrations varied in the range of 230–800 µg/m^3 over the period 1966–88. Lower concentrations (112–484 µg/m^3) were observed in the early 1990s. Geometric mean after-shift urinary concentrations of nickel were in the range of 0.1–0.8 µmol/L (mask in use) and 0.5–1.7 µmol/L (no mask in use). Urinary nickel concentrations were still elevated after 2- and 4-week vacations. No consistent correlations between airborne nickel concentrations and nickel concentrations in the blood or urine were observed.

Thomassen *et al.* (2004) measured the exposure of 135 copper refinery workers (45 females, 90 males) to copper, nickel and other trace elements at a nickel refinery complex in Monchegorsk, the Russian Federation. Full-shift breathing zone samples were collected for workers in the pyrometallurgical process (n = 138) and in the electrorefining process (n = 123) areas. Workers wore personal samplers for two to four full shifts. IOM samplers were used to assess the inhalable aerosol fraction, and Respicon samplers (3-stage virtual impactors) were used to separate the inhalable fraction into respirable, tracheobronchal, and extrathoracic aerosol fractions. The geometric mean inhalable nickel concentration was in the range of 0.024–0.14 mg/m^3 for samples taken in the pyrometallurgical areas, and 0.018–0.060 mg/m^3 for samples taken in the electrorefining areas (data presented as the sum of the inhalable water-soluble and water-insoluble subfractions). For the inhalable aerosol nickel concentrations observed in the pyrometallurgical process steps, the water-insoluble subfraction contained higher levels than the water-soluble fraction, with geometric means of 59 µg/m^3 and 14 µg/m^3, respectively. In the electrorefining process area, the nickel concentrations in the inhalable subfractions were 14 µg/m^3 (water-soluble) and 10 µg/m^3 (water-insoluble).

Air monitoring was conducted in three areas of a nickel base metal refinery in South Africa (the ball mill area, the copper winning area, and the nickel handling area). Personal breathing zone samples (n = 30) were collected in all areas of the

plant, and were analysed gravimetrically and by inductively coupled plasma mass spectroscopy. The mean time-weighted average concentrations for soluble, insoluble and total nickel dust, respectively, were 44, 51, and 95 μg/m^3 in the ball mill area; 395, 400, and 795 μg/m^3 in the nickel handling area; and 46, 17, and 63 μg/m^3 in the copper winning area (Harmse & Engelbrecht, 2007).

Airborne dust concentrations, nickel concentrations, nickel speciation, and aerosol particle size distributions in two large-scale nickel production facilities were assessed by collecting a total of 46 inhalable samples (30 personal, 16 area), and 28 cascade impactor samples (18 personal, 10 area). Samples were collected using IOM and Marple cascade impactor sampling heads, and analysed gravimetrically. At the first site, inhalable concentrations were in the range of 0.5–9.1 mg/m^3 for the personal samples, and 0.2–5.7 mg/m^3 for the area samples (median concentrations, 0.7 mg/m^3 and 0.4 mg/m^3, respectively). Total nickel levels in the personal samples were in the range of 1.8–814.9 μg/m^3, and 19.8–2481.6 μg/m^3 in the area samples (median concentrations, 24.6 μg/m^3 and 92.0 μg/m^3, respectively). At the second site, airborne concentrations of inhalable dust were in the range of 1.2–25.2 mg/m^3 for the personal samples, and 1.5–14.3 mg/m^3 (median concentrations, 3.8 mg/m^3 and 2.9 mg/m^3, respectively) for the area samples. Total nickel levels were in the range of 36.6–203.4 μg/m^3 in the area samples, and 0.2–170.7 μg/m^3 in the personal samples (median concentrations, 91.3 and 15.2 μg/m^3, respectively) (Creely & Aitken, 2008).

(b) Studies of nickel-using industries

Bavazzano *et al.* (1994) collected air, face, hand, and spot urine samples from 41 male workers in electroplating operations in 25 small factories in the province of Florence, Italy, and compared them to samples collected from non-exposed male subjects (face and hand samples: n = 15 subjects aged 15–60 years old; urine samples: n = 60 subjects aged 22–63 years old). For the airborne nickel measurements, personal exposure were in the range of 0.10–42 μg/m^3 (median concentration, 2.3 μg/m^3). The median nickel levels in the urine, on the hands, and on the face were, respectively, 4.2 μg/L (range, 0.7–50 μg/L), 39 μg (range, 1.9–547 μg), and 9.0 μg (range, 1.0–86 μg). Median hand, face, and urine nickel levels for the control subjects were, respectively, 0.8 μg (range, 0.0–5.3 μg; n = 15), 0.30 μg (range, 0.0–2.4; n = 15), and 0.7 μg (range, 0.1–2.5 μg; n = 60).

In an occupational hygiene survey of 38 nickel electroplating shops in Finland, exposure to nickel was assessed by questionnaire (n = 163), urine samples (phase 1: n = 145; phase 2: n = 104), bulk samples (n = 30), and air measurements in three representative shops (one clean, one intermediate, one dirty) on 1 day during which urine samples were also being collected. Full-shift breathing zone samples were collected from inside and outside a respirator with filters. In the first phase of the study, average urinary nickel concentration was 0.16 μmol/L (range, 0.0–5.0 μmol/L; n = 145). The range of mean values for different workplaces was 0.01–0.89 μmol/L, and for the median values, 0.02–0.05 μmol/L. For the 97 workers followed in the second phase, urinary nickel concentrations were observed to fluctuate with exposure, with mean nickel concentrations in the range of 0.10–0.11 μmol/L for the morning specimens, and 0.12–0.16 μmol/L for the afternoon specimens. Personal breathing zone nickel concentrations were as follows: 0.5 μg/m^3 (hanger worker in the 'clean shop'), 0.7 μg/m^3 (worker responsible for maintenance of nickel bath in the 'clean' shop), and in the range of 5.6–78.3 μg/m^3 for workers (n = 6) in the 'dirty' shop. In the area samples, nickel concentrations were 26 μg/m^3 (near the nickel bath in the 'clean' shop), 11.9–17.8 μg/m^3 (in the hanging area of the 'dirty' shop), and 73.3 μg/m^3 (beside the nickel bath in the 'dirty' shop) (Kiilunen *et al.*, 1997).

Kiilunen (1997) analysed data from the biomonitoring registry and the occupational hygiene service registry of the Finnish Institute of Occupational Health to examine trends in nickel exposure during 1980–89. A total of 1795 urinary nickel samples (for which it was possible to identify job titles) were examined, along with 260 nickel measurements from the breathing zone of workers for whom job titles were available. Across all job titles, the ranges of mean urinary nickel concentrations, by time period, were as follows: 0.05–0.52 µmol/L for 1980–82, 0.14–0.51 µmol/L for 1983–85, and 0.17–0.87 µmol/L for 1986–89. The two largest occupational groups sampled were platers (n = 503), and welders (n = 463). Mean urinary concentrations for platers, by time period, were 0.35 µmol/L for 1980–82 (range, 0.01–2.95), 0.30 µmol/L for 1983–85 (range, 0.01–2.10), and 0.38 µmol/L for 1986–89 (range, 0.03–2.37). Mean urinary concentrations for welders, by time period, were 0.22 µmol/L for 1980–82 (range, 0.03–1.58), 0.17 µmol/L for 1983–85 (range, 0.03–0.65), and 0.21 µmol/L for 1986–89 (range, 0.01–1.58). Analysis of the breathing zone measurements revealed that 22.1% of all measurements in 1980–82 had exceeded the occupational exposure limit (OEL) of 0.1 mg/m^3. Similar results were seen for the 1983–85 period (24.8%), rising to 30.7% for the 1986–89 period. Job titles with mean values over the OEL in 1983–85 included: grinders (mean, 0.76 mg/m^3, n = 29), one metal worker (0.12 mg/m^3), powder cutters (mean, 0.34 mg/m^3, n = 31), one spray painter (0.20 mg/m^3), and welders (0.17 mg/m^3, n = 72). Mean levels exceeded the OEL in the following four occupational groups during 1986–89: carbon arc chisellers (mean, 0.6 mg/m^3, n = 2), grinders (mean, 0.28 mg/m^3, n = 19), one warm handler (0.18 mg/m^3), and burn cutters (mean, 0.14 mg/m^3, n = 2).

The association between occupational exposure to airborne nickel and nickel absorption was examined by collecting personal breathing zone samples and urine samples from 10 workers at a galvanizing plant in Brazil that uses nickel sulfate. Spot urine samples were collected pre- and post-shift from the nickel-exposed workers over 5 consecutive days, and from 10 non-nickel exposed workers employed at a zinc plant over 3 consecutive days (n = 97 and 55, respectively). Both groups completed a questionnaire on occupational history, health and lifestyle factors; exposed workers also underwent a medical examination. Personal breathing zone samples (first 4 hours of shift) were collected using NIOSH protocols. Geometric mean airborne nickel levels were in the range of 2.8–116.7 µg/m^3, and the urine levels, from samples taken post-shift, were in the range of 4.5–43.2 µg/g creatinine (mean, 14.7 µg/g creatinine) (Oliveira *et al.*, 2000).

Sorahan (2004) examined data on mean (unadjusted) levels of exposure to inhalable nickel at a nickel alloy plant during 1975–2001 in Hereford, the United Kingdom. Data were reported for two time periods: 1975–80 and 1997–2001. Mean nickel levels (unadjusted) for the earlier period were as follows: 0.84 mg/m^3 in the melting, fettling, and pickling areas; 0.53 mg/m^3 in the extrusion and forge, hot strip and rolling, engineering, and melting stores areas; 0.55 mg/m^3 in the machining, hot rolling, Nimonic finishing, and craft apprentice areas; 0.40 mg/m^3 in the roll turning and grinding, cold rolling, cold drawing, wire drawing, and inspection areas; and 0.04 mg/m^3 in the process stock handling, distribution and warehouse areas. The corresponding mean nickel levels (unadjusted) for the latter period were: 0.37 mg/m^3, 0.45 mg/m^3, 0.31 mg/m^3, 0.30 mg/m^3, and 0.29 mg/m^3, respectively.

Eight-hour TWA (8-h TWA) exposures calculated for the period 1997–2001 were 0.33 mg/m^3, 0.31 mg/m^3, 0.16 mg/m^3, 0.16 mg/m^3, and 0.27 mg/m^3, respectively.

Sorahan & Williams (2005) assessed the mortality of workers at a nickel carbonyl refinery in Clydach, the United Kingdom to determine whether occupational exposure to nickel resulted in increased risks of nasal cancer and lung cancer.

Using personal sampling data collected in the 1980s and 1990s, 8-h TWA exposure to total inhalable nickel was calculated, and assigned to six categories of work, based on the predominant species of nickel exposure. The six categories of work were: feed handling and nickel extraction, including kilns (oxide/metallic); pellet and powder production, and shipping (metallic); nickel salts and derivatives, and effluent (metallic/soluble); wet treatment and related processes (metallic/subsulfide/soluble); gas plant (non-nickel); and engineering and site-wide activities that could include any of the preceding work areas. Mean levels of total inhalable nickel dust were in the range of 0.04–0.57 mg/m^3 in the 1980s (n = 1781), and 0.04–0.37 mg/m^3 in the 1990s (n = 1709).

Stridsklev *et al.* (2007) examined the relationship between the concentration of airborne nickel in the occupational environment of grinders (n = 9) grinding stainless steel in Norway and the concentration of nickel in their urine and blood. Grinders either worked in a well ventilated hall of a shipyard or in a small non-ventilated workshop. The sampling protocol was as follows: full-shift personal samples were collected in the breathing zone of grinders over the course of 1 work week; urine samples were collected three times daily for 1 week (first void in the morning, pre- and post-shift); and blood samples were drawn twice daily for 3 days in 1 week (pre- and post-shift). Blood and urine samples were also collected on the Monday morning after a 3-week vacation in the workshop. Grinders also completed a questionnaire to collect information on work history, use of personal protective equipment, and smoking habits. Mean levels of airborne nickel were 18.9 µg/m^3 (range, 1.8–88.6 µg/m^3) in the shipyard, and 249.8 µg/m^3 (range, 79.5–653.6 µg/m^3) in the workshop. Mean blood nickel levels for grinders were 0.87 µg/L (range, < 0.8–2.4 µg/L) in whole blood, and 1.0 µg/L (range, < 0.4–4.1 µg/L) in plasma. Mean urinary nickel levels for grinders were 3.79 µg/g creatinine (range, 0.68–10.6 µg/g creatinine), 3.39 µg/g creatinine (range, 0.25–11.1 µg/g creatinine), and 4.56 µg/g creatinine (range, < 0.53–11.5 µg/g creatinine), from the first void, pre- and post-shift samples, respectively. With the exception of stainless steel welders welding the MIG/MAG-method [Metal Inert Gas-Metal Active Gas], mean urinary nickel levels were higher in grinders than in welders. Mean urinary nickel levels in MIG/MAG welders were 5.9 µg/g creatinine (range, < 0.24–20.5 µg/g creatinine), 3.8 µg/g creatinine (range, 0.33–11.4 µg/g creatinine), and 4.6 µg/g creatinine (range, < 0.25–18.4 µg/g creatinine) from the first void, pre-, and post-shift samples, respectively.

Sivulka & Seilkop (2009) reconstructed historical exposures to nickel oxide and metallic nickel in the US nickel alloy industry from personal and area measurements collected at 45 plants since the 1940s (n = 6986 measurements). Of the measurements included in the database, 96% were personal breathing zone samples, and 4% were stationary area samples. The data provided evidence of a strongly decreasing gradient of airborne total nickel levels from the 1940s to the present.

1.5.3 Dietary exposure

Nickel has been measured in a variety of foodstuffs as "total nickel." Average concentrations are in the range of 0.01–0.1 mg/kg, but can be as high as 8–12 mg/kg in certain foods (EVM, 2002; WHO, 2007). Factors influencing the concentration of nickel in food include the type of food (e.g. grains, vegetables, fruits versus seafood, mother's milk versus cow's milk), growing conditions (i.e. higher concentrations have been observed in food grown in areas of high environmental or soil contamination), and food preparation techniques (e.g. nickel content of cooking utensils, although the evidence for leaching from stainless steel cookware is somewhat mixed) (EVM, 2002; WHO, 2007).

The highest mean concentrations of nickel have been measured in beans, seeds, nuts and grains (e.g. cocoa beans, 9.8 µg/g; soyabeans, 5.2 µg/g; soya products, 5.1 µg/g; walnuts, 3.6 µg/g; peanuts, 2.8 µg/g; oats, 2.3 µg/g; buckwheat, 2.0 µg/g; and oatmeal, 1.8 µg/g). Although nickel concentrations vary by type of foodstuff, average levels are generally within the range of 0.01–0.1 µg/g. Reported ranges for some common food categories are: grains, vegetables and fruits, 0.02–2.7 µg/g; meats, 0.06–0.4 µg/g; seafood, 0.02–20 µg/g; and dairy, < 100 µg/L (EVM, 2002). This variability in nickel content makes it difficult to estimate the average daily dietary intake of nickel (EVM, 2002).

1.5.4 Biomarkers of exposure

Biomarker levels are influenced by the chemical and physical properties of the nickel compound studied, and by the time of sampling. It should be noted that the nickel compounds, the timing of collection of biological samples (normally at the end of a shift), and the analytical methods used differ from study to study, and elevated levels of nickel in biological fluids and tissue samples are mentioned only as indications of uptake of nickel, and may not correlate directly to exposure levels (IARC, 1990).

Atomic absorption spectrometry (AAS) and inductively coupled plasma atomic emission spectroscopy (ICP-AES) are the most common analytical methods used to determine "total nickel" concentrations in biological materials (such as blood, tissues, urine, and faeces). Nickel content can also be measured in other tissues, such as nails and hair, although specific procedures for dissolving the sample must be followed (ATSDR, 2005). The presence of calcium, sodium or potassium interferes with the quantification of nickel in biological samples, and specific techniques (e.g. isotope dilution) must be used to validate nickel measurements (ATSDR, 2005). Serum and urine samples are the most useful biomarkers of recent exposure, reflecting the amount of nickel absorbed in the previous 24–48 hours (NTP, 2000).

Minoia *et al.* (1990) used atomic absorption spectroscopy and neutron activation analysis to determine trace element concentrations of nickel in urine, blood, and serum collected from non-exposed healthy subjects (n = 1237; 635 males, 602 females) from the Lombardy region of northern Italy. The mean nickel level in urine samples (n = 878) was 0.9 µg/L (range, 0.1–3.9 µg/L); in blood samples (n = 36), 2.3 µg/L (range, 0.6–3.8 µg/L); and in serum samples (n = 385), 1.2 µg/L (range, 0.24–3.7 µg/L).

In a Norwegian-Russian population-based health study, human nickel exposure was investigated in the adult population living near a nickel refinery on both sides of the Norwegian-Russian border during 1994–95. Urine samples were collected from inhabitants, aged 18–69 years, of Nikel, Zapolyarny, and Sor-Varanger and also from individuals living more remotely from the Kola Peninsula nickel-producing centres (in the Russian cities of Apatity and Umba, and the Norwegian city of Tromso). A total of 2233 urine specimens were collected and analysed for nickel using electrothermal atomic absorption spectrometry. The highest urinary nickel concentrations were observed in residents of Nikel (median, 3.4 µg/L; mean, 4.9 µg/L; range, 0.3–61.9 µg/L), followed by Umba (median, 2.7 µg/L; mean, 4.0 µg/L; range, 1.0–17.0 µg/L), Zapolyarny (median, 2.0 µg/L; mean, 2.8 µg/L; range, 0.3–24.2 µg/L), Apatity (median, 1.9 µg/L; mean, 2.6 µg/L; range, 0.3–17.0 µg/L), Tromso (median, 1.2 µg/L; mean, 1.4 µg/L; range, 0.3–6.0 µg/L), and Sor-Varanger (median, 0.6 µg/L; mean, 0.9 µg/L; range, 0.3–11.0 g/L). The Russian participants all had a higher urinary nickel average than those from Norway, regardless of geographic location (Smith-Sivertsen *et al.*, 1998).

Ohashi *et al.* (2006) determined reference values for nickel in urine among women of the general population of 11 prefectures in Japan.

A total of approximately 13000 urine samples were collected in 2000–05 from 1000 adult women aged 20–81 years who had no occupational exposure to nickel. Nickel in urine was analysed by graphite furnace atomic absorption spectrometry. The observed geometric mean concentration for nickel was 2.1 µg/L (range, < 0.2–57 µg/L). After correction for creatinine, the geometric mean concentration was reported as 1.8 µg/L (maximum, 144 µg/L).

1.5.5 Other sources of exposure

Nickel, chromium, and cobalt are common causes of allergic contact dermatitis. In the early 1990s it was recommended that household and other consumer products should not contain more than 5 ppm of each of nickel, chromium, or cobalt, and that, for an even greater degree of protection, the ultimate target level should be 1 ppm. In a recent survey, selected consumer products had the following nickel levels (ppm): hand-wash powders, 0.9; heavy duty powders, 0.5; laundry tablets, 0.5; liquid/powder cleaners, 0.4; heavy duty liquids, 0.1; machine/hand-wash liquids, 0.1; hand-wash liquids, 0.1, fine wash liquids, 0.1; and dishwashing liquids, 0.1 (Basketter *et al.*, 2003).

Potential iatrogenic sources of exposure to nickel are dialysis treatment, leaching of nickel from nickel-containing alloys used as prostheses and implants, and contaminated intravenous medications (Sunderman, 1984).

2. Cancer in Humans

The previous *IARC Monograph* was based upon evidence of elevated risk of lung and nasal cancers observed among workers involved in a variety of nickel sulfide ore smelting and nickel refining processes that included high-temperature processing of nickel matte, nickel–copper matte, electrolytic refining, and Mond process refining. The exposures included metallic nickel, nickel oxides, nickel subsulfide, soluble nickel compounds, and nickel carbonyl. These cohort studies were conducted mainly in Canada, Norway, Finland, and in the United Kingdom (IARC, 1990; ICNCM, 1990).

2.1 Cohort studies and nested case–control studies

Since the previous *IARC Monograph*, several studies have extended follow-up to some of the previous cohorts, and have provided additional cohort and nested case–control analyses related mostly to lung cancer risk, and taking into account potential confounding factors as well as mixed exposures to water-soluble and -insoluble nickel compounds. Among the most common occupations with exposure to nickel compounds are stainless steel welders, who are also exposed to chromium (VI) compounds, and other compounds. Although there have been some cohort studies of stainless steel welders, these are not recorded in the present *Monograph* because it is difficult to ascribe any excess risks in these cohorts to nickel compounds specifically. Key results of some of these cohort studies can be found in Table 2.1 of the *Monograph* on chromium (VI) in this volume.

Also, since the previous *IARC Monograph*, experimental evidence has become available that nickel metal dust can become solubilized and bioavailable after inhalation. Consequently, separately classifying nickel and nickel compounds was viewed by the Working Group as not warranted. A similar distinction has not been made for other metals, e.g. beryllium and cadmium, in other *IARC Monographs*. Accordingly, this review did not exclude studies that focused on metallic nickel, unless they, for other reasons, were considered uninformative.

2.1.1 Cancer of the lung

Studies were carried out in nickel smelters and refineries in Canada, Norway (Kristiansand), Finland, and the United Kingdom (Clydach). Because the refining processes differed in the plants, the exposure profiles to various nickel compounds were different across the cohorts. Nonetheless, increased risks for lung cancer were found in cohorts from all of these facilities (see Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-05-Table2.1.pdf).

High risks for lung cancers were observed among calcining workers in Canada, who were heavily exposed to both sulfidic and oxidic nickel (nickel sulfides and oxides). A high lung cancer rate was also seen among nickel plant cleaners in Clydach who were heavily exposed to these insoluble compounds, with little or no exposure to soluble nickel. The separate effects of oxides and sulfides could not be estimated, however, as high exposure was always either to both, or to oxides together with soluble nickel. Workers in Clydach calcining furnaces and nickel plant cleaners, exposed to high levels of metallic nickel, had high lung cancer risks (see Table 2.1 online). A substantial excess risk for lung cancer among hydrometallurgy workers in Norway was mainly attributed to their exposure to water-soluble nickel. Their estimated exposures to other types of nickel (metallic, sulfidic, and oxidic) were as much as an order of magnitude lower than those in several other areas of the refinery, including some where cancer risks were similar to those observed in hydrometallurgy. High risks for lung cancer were also observed among electrolysis workers at Kristiansand (Norway). These workers were exposed to high estimated levels of soluble nickel and to lower levels of other forms of nickel. Nickel sulfate and nickel chloride (after 1953) were the only or predominant soluble nickel species present in these areas.

An update of the Kristiansand cohort by Andersen *et al.* (1996) demonstrated a dose–response relationship between cumulative exposure to water-soluble nickel compounds and lung cancer ($P < 0.001$) when adjustment was made for age, smoking, and nickel oxide. The risk was increased 3-fold in the highest soluble nickel dose group. A lesser, but positive, effect was seen between cumulative exposure to nickel oxide and risk of lung cancer, also with adjustment for age, cigarette smoking, and exposure to water-soluble nickel (P for trend = 0.05, see Table 2.2).

Subsequent to the Andersen *et al.* (1996) study, an industrial hygiene study re-evaluated exposure among the Norwegian refinery workers based on new information related to nickel species and exposure levels (Grimsrud *et al.*, 2000). Grimsrud *et al.* (2003) updated the lung cancer incidence among the Norwegian nickel refinery workers (see Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-05-Table2.3.pdf). The strongest gradient for cumulative exposure and lung cancer was found in relation to water-soluble nickel adjusted for cigarette-smoking habits, which was known for 4728 (89%) of the cohort members. Regarding species of water-soluble nickel compounds, the risk from potential exposure to nickel chloride was similar to that for nickel sulfate. The nickel electrolysis process (using nickel sulfate) changed to a nickel-chloride-based process in 1953, and workers hired in 1953 or later had a similar lung cancer risk (standardized incidence ratio [SIR], 4.4; 95%CI: 1.8–9.1) as for those employed in the same area before 1953 when the nickel sulfate was used (SIR, 5.5; 95%CI: 3.0–9.2). Analyses by year of first employment indicated that those initially employed after 1978 continued to demonstrate a significantly elevated risk of lung cancer (SIR, 3.7; 95%CI: 1.2–8.7), suggesting continued exposure to nickel compounds.

Grimsrud *et al.* (2002) conducted a case–control study of lung cancer nested within the

Table 2.2 Relative risks of lung cancer by cumulative exposure to soluble nickel and nickel oxide, considering the two variables simultaneously by multivariate Poisson regression analysis[a]

Variable	Mean exposure (mg/m^3)	Cases	Relative risk	95%CI	Test for linear trend
Soluble nickel					$P < 0.001$
< 1	0.1	86	1.0	Referent	
1–4	2.3	36	1.2	0.8–1.9	
5–14	8.8	23	1.6	1.0–2.8	
≥ 15	28.9	55	3.1	2.1–4.8	
Nickel oxide					$P = 0.05$
< 1	0.4	53	1.0	Referent	
1–4	2.5	49	1.0	0.6–1.5	
5–14	8.3	53	1.6	1.0–2.5	
≥ 15	44.3	45	1.5	1.0–2.2	

[a] Workers with unknown smoking habits were excluded (three cases of lung cancer).
Adjusted for smoking habits and age.
From Andersen *et al.* (1996)

cohort of Norwegian nickel refinery workers (see Table 2.3 online). Exposure groups were determined based on quintiles of the exposure variables in the controls. Analyses by cumulative exposure adjusted for cigarette smoking indicated that odds ratios for lung cancer in the highest cumulative exposure category of water-soluble nickel, sulfidic nickel, metallic nickel, and oxidic nickel were 3.8 (95%CI: 1.6–9.0), 2.8 (95%CI: 1.1–6.7), 2.4 (95%CI: 1.1–5.3), and 2.2 (95%CI: 0.9–5.4), respectively. The trend for cumulative exposure and lung cancer was significant for water-soluble nickel compounds only ($P = 0.002$). There was, however, a high degree of correlation with exposure to nickel and nickel compounds as a whole, making evaluation of the independent effect of individual compounds difficult. Nonetheless, when data were further adjusted for exposure to water-soluble compounds, there were no significant trends in the odds ratios by cumulative exposure to sulfidic, oxidic, or metallic nickel. The odds ratios related to the highest cumulative exposure group for each of these compounds were 1.2 (95%CI: 0.5–3.3), 0.9 (95%CI: 0.4–2.5), and 0.9 (95%CI: 0.3–2.4), respectively (see Table 2.4). In further analyses, with adjustment for cigarette smoking, arsenic, asbestos, sulfuric acid mist, cobalt and occupational carcinogenic exposures outside the refinery, the strong association between lung cancer and water-soluble nickel remained (Grimsrud *et al.*, 2005).

Anttila *et al.* (1998) updated an earlier cohort study of Finnish nickel refinery and copper/nickel smelter workers (Karjalainen *et al.*, 1992). Among refinery workers employed after 1945, who were exposed primarily to nickel sulfate, an excess of lung cancer was observed in the overall cohort (SIR, 2.61; 95%CI: 0.96–5.67), and the lung cancer risk increased with > 20 years of latency (SIR, 3.38; 95%CI: 1.24–7.36, based on six cases). Among smelter workers, lung cancer was also elevated in the overall cohort (SIR, 1.39; 95%CI: 0.78–2.28), and, similarly, a significant increase in lung cancer risk with > 20 years of latency was observed (SIR, 2.00; 95%CI: 1.07–3.42).

There have been three subsequent reports that provide additional information on refinery workers in Wales (the United Kingdom) exposed to nickel carbonyl and other nickel compounds.

Easton *et al.* (1992) carried out an updated analysis of Welsh nickel refinery workers to determine which nickel compounds were responsible for lung cancer among the 2524 workers employed

Table 2.4 Adjusted[a] odds ratios for lung cancer by exposure to sulfidic, oxidic or metallic nickel in a nested case–control study of Norwegian nickel refinery workers observed during 1952–95

Cumulative exposure to nickel[b]	Odds ratio	95% CI
Sulfidic nickel		
Unexposed	1.0	
Low	1.5	0.6–3.9
Low-medium	2.2	0.9–5.5
Medium	1.8	0.7–4.5
Medium-high	1.3	0.5–3.3
High	1.2	0.5–3.3
Likehood ratio test: $P = 0.344$		
Oxidic nickel		
Unexposed	1.0	
Low	1.5	0.6–3.8
Low-medium	1.8	0.7–4.5
Medium	1.4	0.6–3.7
Medium-high	1.5	0.6–3.7
High	0.9	0.4–2.5
Likehood ratio test: $P = 0.406$		
Metallic nickel		
Unexposed	1.0	
Low	1.2	0.5–2.9
Low-medium	1.0	0.5–2.4
Medium	1.0	0.4–2.3
Medium-high	1.0	0.4–2.4
High	0.9	0.3–2.4
Likehood ratio test: $P = 0.972$		

[a] Data were adjusted for smoking habits in five categories (never smoker, former smoker, or current smoker of 1–10, 11–20, or > 20 g/day), and for exposure to water-soluble nickel as a continuous variable with natural log-transformed cumulative exposure values (ln[(cumulative exposure) + 1]).

[b] Categories were generated according to quartiles among exposed control. In each of the three analyses, data were unadjusted for the other two insoluble forms of nickel.

From Grimsrud *et al.* (2002)

for > 5 years before the end of 1969, and followed during 1931–85. The model was based on exposures occurring before 1935, and was adjusted for age at first exposure, duration of exposure, and time since first exposure. For lung cancer, the best fitting model suggested risks for soluble and metallic nickel exposures, and much less (if any) risk for nickel oxide or sulfides. Sorahan & Williams (2005) followed during 1958–2000 a group of 812 workers from the cohort of Welsh nickel refinery workers who were hired between 1953–92, and who had achieved > 5 years of employment. The overall lung cancer SMR was 1.39 (95%CI: 0.92–2.01). For those with > 20 years since the start of employment, lung cancer risk was significantly elevated [SMR, 1.65; 95%CI: 1.07–2.41], indicating an elevated risk of lung cancer among those hired since 1953.

Grimsrud & Peto (2006) combined data from the most recent updates of Welsh nickel refinery workers to assess lung cancer mortality risk by period of initial employment. For those first employed since 1930, an elevated risk was observed for lung cancer (SMR, 1.33; 95%CI: 1.03–1.72). [The Working Group noted that

exposures were dramatically reduced during the 1920s.]

Egedahl *et al.* (2001) updated the mortality data among employees at a hydrometallurgical nickel refinery and fertilizer complex in Fort Saskatchewan, Canada, who had worked for 12 continuous months during 1954–78. Among the 718 men exposed to nickel, the lung cancer SMR was 0.67 (95%CI: 0.24–1.46, based on six deaths). Significant decreases were observed for the 'all causes of death' category (SMR, 0.57; 95%CI: 0.43–0.74), and for the 'all cancer deaths' category (SMR, 0.47; 95%CI: 0.25–0.81). [The Working Group considered the study uninformative for the evaluation of cancer risks due to a substantial healthy worker effect which may have masked excess mortality that was associated with nickel exposure.]

Goldberg *et al.* (1994) conducted a 10-year incidence study and a nested case–control study of a cohort of nickel mining (silicate-oxide ores) and refinery workers in New Caledonia, South Pacific. They observed a significant decrease in the incidence of lung cancer, and this was also observed for other respiratory cancers The results of the case–control study did not show elevated risks for respiratory cancers in relation to low levels of exposure to soluble nickel, nickel sulfide, or metallic nickel. For all three nickel exposures separately, the odds ratios were 0.7.

[The Working Group noted that in most of these studies of lung cancer risk in smelters and refineries, there was exposure to metallic nickel together with exposure to the other forms of nickel (Sivulka, 2005). Only one of these studies involved an attempt to evaluate separately the effect of metallic nickel (Grimsrud *et al.*, 2002).]

Several additional studies of workers with potential exposure to metallic nickel were reviewed by the Working Group. Arena *et al.* (1998) evaluated mortality among workers exposed to "high nickel alloys" in the USA. A recent industrial hygiene analysis indicated that oxidic nickel comprised 85% of the total nickel exposure of these workers, with the rest being mostly metallic nickel (Sivulka & Seilkop, 2009). Compared to US national rates, lung cancer was significantly elevated among white men (SMR, 1.13; 95%CI: 1.05–1.21), among non-white men the SMR was 1.08 (95%CI: 0.85–1.34), and in women 1.33 (95%CI: 0.98–1.78). [The Working Group noted that the lung cancer SMR for the entire cohort combined was 1.13 (95%CI: 1.06–1.21) based on 955 observed deaths.] The authors also calculated SMRs based on local (SMSA) rates for the separate population subgroups. When calculated for the total cohort, the resulting SMR was [1.01; 95%CI: 0.95–1.08]. [The Working Group noted that it is difficult to interpret the use of local rates when the study population was derived from 13 separate areas located throughout the USA, but the use of rates from urban areas could have overestimated the expected number of deaths from lung cancer. The Working Group noted that the overall SMR for lung cancer in this study compared with the national population was statistically significant, and provides some evidence of an association between exposures in these plants and lung cancer. It appears that the primary exposure was to nickel oxide and thus, the study cannot be used to evaluate the specific carcinogenicity of metallic nickel. Analysis of lung cancer by duration of employment did not indicate a dose–response. The Working Group noted that duration of employment is a poor measure of exposure when exposures are known to have declined over time.]

There have also been a series of studies conducted in the French stainless steel industry that involved co-exposure to several known and potential human lung carcinogens, and the most detailed exposure assessment considered nickel and chromium combined (Moulin *et al.* 1990, 1993a, b, 1995, 2000).]

The only cohort of workers exposed to metallic nickel in the absence of other nickel compounds (Oak Ridge cohort) included only 814 workers, and provided little statistical power to evaluate

lung cancer risk (Godbold & Tompkins, 1979; Cragle *et al.*, 1984).

Sorahan (2004) updated the mortality rate among employees manufacturing nickel alloys at the plant in Hereford, the United Kingdom. The study showed a significant decrease for 'all causes of death' (SMR, 0.79), for 'all cancer deaths' (SMR, 0.81), and a non-significant decrease for lung cancer (SMR, 0.87; 95%CI: 0.67–1.11).

Pang *et al.* (1996) evaluated cancer risks among 284 men who were employed for at least 3 months during 1945–75 in a nickel-plating department, and followed through 1993. For lung cancer, the overall SMR was 1.08 (95%CI: 0.54–1.94). For those with > 20 years latency, eight lung cancer deaths were observed versus 6.31 expected [SMR, 1.27; 95%CI: 0.55–2.50].

Several other studies reviewed by Sivulka (2005) had mixed exposure to metallic nickel and other nickel compounds, and provide no evidence on the carcinogenicity of metallic nickel alone. Furthermore, many of the studies cited in the review involved mixed exposures in stainless steel welding and grinding, and manufacturing nickel alloys (Cox *et al.*, 1981; Enterline & Marsh, 1982; references from Tables 5 and 6 of Sivulka, 2005), and therefore were not considered relevant for evaluating the carcinogenicity of nickel and/or nickel compounds.

2.1.2 Cancer of the nasal cavity

Increased risks for nasal cancers were found to be associated with exposures during high-temperature oxidation of nickel matte and nickel-copper matte (roasting, sintering, calcining) in cohort studies in Canada, Norway (Kristiansand), and the United Kingdom (Clydach), with exposures in electrolytic refining in a study in Norway, and with exposures during leaching of nickel-copper oxides in acidic solution (copper plant), and extraction of nickel salts from concentrated solution (hydrometallurgy) in the United Kingdom (see Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-05-Table2.5.pdf).

In the Norwegian study, Andersen *et al.* (1996) demonstrated a dose–response relationship between both cumulative exposure to water-soluble nickel and nickel oxide compounds and the risk of nasal cancer. The SIR (compared to the general population) was the highest in the group of workers with the highest cumulative exposure to soluble nickel compounds combined with insoluble nickel compounds (SIR, 81.7; 95%CI: 45–135; based on 15 cases). For workers with the highest cumulative exposure to nickel oxide, the SIR was 36.6 (95%CI: 19.5–62.5; based on 13 cases) (see Table 2.6 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-05-Table2.6.pdf).

An update of nasal cancer in Finnish refinery workers after 20 years since the first exposure to nickel reported an SIR of 67.1 (95%CI: 12–242.0; based on two cases) (Anttila *et al.*, 1998). An additional nasal cancer was observed 2 years after the follow-up period ended, and a fourth potential nasal cancer (classified as a nasopharyngeal cancer, 0.04 expected) was reported during the follow-up period. No nasal cancers were observed among the smelter workers who were exposed primarily to nickel matte, nickel subsulfide, nickel sulfides, and other metals.

Easton *et al.* (1992) attempted to identify the nickel compounds responsible for nasal cancer among 2524 Welsh nickel refinery workers employed for > 5 years before the end of 1969, and followed during 1931–85. As shown in Table 2.7, the risk for nasal cancer was in the range of 73–376 times the expected for those first employed before 1930, based on 67 nasal cancer deaths. A statistical model that fitted to the data on men whose exposures occurred before 1935, and that adjusted for age at first exposure, duration of exposure, and time since first exposure indicated that the soluble nickel effect on nasal cancer risk is the only one significant.

Table 2.7 Observed and expected deaths from nasal sinus cancer (1931–85) by year of first employment

Year first employed	Observed deaths	Expected deaths	SMR	95% CI
< 1920	55	0.15	376	276–477
1920–29	12	0.17	73	36–123
1930–39	1	0.07	14	0.4–80
1940–49	0	0.06	–	–
> 1950	0	0.06	–	–
Total	68	0.45	151	117–192

From Easton *et al.* (1992)

Grimsrud & Peto (2006) combined data from the most recent updates of Welsh nickel refinery workers to assess nasal cancer mortality risk by period of initial employment. For those first employed since 1930, an elevated risk was observed for nasal cancer (SMR, 8.70; 95%CI: 1.05–31.41, based on two observed deaths).

In one study of Swedish Ni–Cd battery workers, three nasal cancer cases versus 0.36 expected were observed (SIR, 8.32; 95%CI: 1.72–24.30) (Järup *et al.*, 1998). Two of these cases occurred among workers exposed to greater than 2 mg/m^3 nickel (SIR, 10.8; 95%CI: 1.31–39.0).

2.1.3 Other cancer sites

Other than for lung cancer and nasal sinus cancer, there is currently no consistency in the epidemiological data to suggest that nickel compounds cause cancer at other sites.

The results of several studies of workers exposed to nickel compounds showed a statistically elevated risk of a site-specific cancer in addition to lung and nasal cancer. A study of sinter plant workers in Canada showed a significantly elevated risk of cancer of the buccal cavity and pharynx (IARC, 1990). In a study in the Norwegian nickel-refining industry, a significant excess of laryngeal cancer was observed among roasting and smelter workers (Magnus *et al.*, 1982).

Stomach cancer was significantly elevated among men employed in a nickel- and chromium-plating factory in the United Kingdom (Burges, 1980). A study of men employed in a nickel-plating department (Pang *et al.*, 1996) showed a significant elevation in stomach cancer. Another study (Anttila *et al.*, 1998) demonstrated a significant excess of stomach cancer among nickel refinery workers.

A study of workers producing alloys with a high nickel content (Arena *et al.*, 1998) demonstrated a significant excess of colon cancer among 'non-white males' (relative risk, 1.92; 95%CI: 1.28–2.76), and a 2-fold risk of kidney cancer among white males employed in 'melting.' However, the excess risk was not associated with length of employment or time since first employment. [The Working Group noted that specific data was not provided in the article.]

A meta-analysis (Ojajärvi *et al.*, 2000) reported a significantly elevated risk for pancreatic cancer that upon further evaluation actually indicated no elevation in risk (Seilkop, 2002).

A population-based case–control study (Horn-Ross *et al.*, 1997) based on self-reported occupational exposure, showed a dose–response relationship between cumulative exposure to nickel compounds/alloys and salivary gland cancer. [The Working Group noted that the author corrected the direction of signs in Table 2 of her report in a subsequent erratum.]

2.2 Synthesis

The Working Group evaluated a large body of evidence and concluded that there is an elevated risk of lung and nasal sinus cancer among nickel refinery workers (IARC, 1990; Andersen *et al.*, 1996; Anttila *et al.*, 1998; Grimsrud & Peto, 2006), and an elevation in lung cancer risk among nickel smelter workers (IARC, 1990; Anttila *et al.*, 1998).

Epidemiological studies have provided evidence for lung cancer related to specific nickel compounds or classes of compounds (based, for example, on water solubility). Evidence for elevated risk of lung cancer in humans was demonstrated specifically for nickel chloride (Grimsrud *et al.*, 2003), nickel sulfate, water-soluble nickel compounds in general (Andersen *et al.*, 1996; Grimsrud *et al.*, 2002, 2003; Grimsrud *et al.*, 2005), insoluble nickel compounds, nickel oxides (Andersen *et al.*, 1996; Anttila *et al.*, 1998; Grimsrud *et al.*, 2003), nickel sulfides (Grimsrud *et al.*, 2002), and mostly insoluble nickel compounds (Andersen *et al.*, 1996).

A study that modelled risks of various nickel compounds and lung cancer risk identified both water-soluble nickel and metallic nickel as contributing to risk (Easton *et al.*, 1992). The largest study addressing worker exposure to metallic nickel (in combination with nickel oxide) showed a small but significant elevation in lung cancer risk (Arena *et al.*, 1998).

Other studies specifically addressing nickel metal exposures were uninformative and did not allow any judgment as to whether such exposures should be considered different with regard to cancer risk. It was not possible to entirely separate various nickel compounds in dose–response analyses for specific nickel compounds. In one analysis, an additional adjustment for water-soluble nickel compounds on risk of lung cancer indicated little association with cumulative exposure to sulfidic, oxidic or metallic nickel. One study of Ni–Cd battery workers exposed to nickel hydroxide and cadmium oxide demonstrated a significant risk of cancer of the nose and nasal sinuses.

On the basis of the Norwegian studies of refinery workers, the evidence is strongest for water-soluble nickel compounds and risk for lung cancer. The confidence of the Working Group in the above findings was reinforced by the availability of information on cigarette smoking for 89% of the Norwegian cohort, and the adjustments made for potential confounding exposures.

3. Cancer in Experimental Animals

Nickel and nickel compounds have been tested for carcinogenicity by intramuscular injection to rats, mice, and rabbits; by repository injections at multiple sites in hamsters, rabbits and mice; by intraperitoneal administration to rats and mice; and by intratracheal instillation, intrapleural, intrarenal, intraocular, inhalation, and subcutaneous exposure to rats.

Particularly relevant studies reviewed in the previous *IARC Monograph* (IARC, 1990) were reconsidered in this evaluation, and summarized in the text.

3.1 Oral administration

3.1.1 Nickel sulfide

In a 2-year multiple dose study, oral nickel sulfate hexahydrate given to male and female rats did not result in carcinogenesis (Heim *et al.*, 2007).

3.1.2 Nickel chloride

Nickel chloride was tested for carcinogenicity by oral administration in female hairless mice (CRL: SK1-hrBR). Mice were exposed to ultraviolet radiation (UVR) alone, nickel chloride alone (given in the drinking-water) and UVR + various concentrations of nickel chloride. Nickel

Table 3.1 Studies of cancer in experimental animals exposed to nickel compounds (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M, F) 104 wk Heim *et al.* (2007)	Nickel sulfate hexahydrate 0, 10, 30, 50 mg/kg/d (gavage),[a] 60/group/sex	Keratoacanthoma (tail): M–low dose 15% (numbers not provided)	$P < 0.001$	Age at start, 6 wk 99.9% pure Exposure-related decreased bw in males and females (2 highest dose groups) Exposure-related increased mortality ($P_{trend} < 0.008$) in high dose females but not males
Mouse, CRL: Sk1-hrBR (F) 224 d Uddin *et al.* (2007)	Nickel chloride in drinking-water at 3 wk of age 3 wk later UV treatment (1.0 kJ/m^2) 3 d/wk for 26 wk Groups, number of animals Group 1: Controls, 5 Group 2: UV only, 10 Group 3: 500 ppm, 10 Group 4: UV + 20 ppm, 10 Group 5: UV + 100 ppm, 10 Group 6: UV + 500 ppm, 10 5–10/group	Skin (tumours): Number of tumours/mice at 29 wk Group 1: 0 Group 2: 1.7 ± 0.4 Group 3: 0 Group 4: 2.8 ± 0.9 Group 5: 5.6 ± 0.7 Group 6: 4.2 ± 1.0	Group 5 vs Group2 $P < 0.05$ Group 6 vs Group 2 $P < 0.05$	Age at start, 3 wk Nickel had no effect on growth of the mice Nickel levels in skin increased with dose

[a] vehicle not stated

d, day or days; F, female; M, male; UVR, ultraviolet radiation; vs, versus; wk, week or weeks

chloride alone did not cause skin tumours by itself, but when combined with UVR, it increased the UVR-induced skin tumour incidence (Uddin *et al.*, 2007).

See Table 3.1.

3.2 Inhalation exposure

3.2.1 Nickel sulfate hexahydrate

Nickel sulfate hexahydrate was not shown to be carcinogenic in male or female rats or male or female mice when given by inhalation in a 2-year bioassay study (Dunnick *et al.*, 1995; NTP, 1996a). Analysis of lung burden showed that nickel was cleared from the lungs (Dunnick *et al.*, 1995).

3.2.2 Nickel subsulfide

Nickel subsulfide induced lung tumours in rats exposed by inhalation (Ottolenghi *et al.*, 1975).

Inhalation of nickel subsulfide increased the incidence of aveolar/bronchiolar adenomas and carcinomas in male F344 rats, and increased combined lung tumours in females (Dunnick *et al.*, 1995; NTP, 1996b). Nickel subsulfide also increased the incidence of adrenal pheochromocytomas (benign or malignant) in male and female rats, malignant pheochromocytomas were increased in male rats. Significant dose-related trends were observed for both lung and adrenal tumours in both sexes.

3.2.3 Nickel oxide

The carcinogenicity of nickel oxide was investigated in 2-year inhalation studies in F344 male and female rats, and B6C3F$_1$ male and female mice. Nickel oxide induced tumours of the lung (aveolar bronchiolar adenomas or carcinomas), and adrenal medulla (malignant and benign pheochromocytoma) in both sexes of rats. Nickel oxide also increased the incidence of lung tumours in low-dose females but not in male mice (NTP, 1996c).

3.2.4 Metallic nickel

Inhaled metallic nickel increased the incidence of adrenal pheochromocytomas (benign, malignant, and benign and malignant combined) in male rats and adrenal cortex tumours in female rats (Oller *et al.*, 2008). Dose-related responses were observed for both types of adrenal tumours. No significant increases in lung tumours occurred. Elevated blood levels of nickel indicated that metallic nickel was bioavailable systematically after inhalation (Oller *et al.*, 2008).

3.2.5 Other forms of nickel

Nickel carbonyl induced lung carcinomas after inhalation exposure (Sunderman *et al.*, 1957, 1959).

See Table 3.2.

3.3 Parenteral administration

3.3.1 Nickel subsulfide

(a) Mouse

Nickel subsulfide induced local sarcomas after repository injections at multiple sites in numerous studies in mice (IARC, 1990).

No increase in lung tumour incidence was observed in male strain A/J mice, 20 or 45 weeks after exposure to various treatment regimens of nickel subsulfide (McNeill *et al.*, 1990). In another study, nickel subsulfide induced injection-site tumours in all three strains of mice, with the order of susceptibility to tumour formation being C3H, B6C3F$_1$, and C57BL6 (Rodriguez *et al.*, 1996). Waalkes *et al.* (2004, 2005) studied the carcinogenic response to nickel subsulfide in MT-transgenic and MT-null mice. Intramuscular administration of nickel subsulfide increased the incidence of injections-site tumours (primarily fibrosarcoma) in MT-transgenic and concordant wild-type mice, and lung tumours in MT-transgenic mice (Waalkes *et al.*, 2004). In MT-null mice and concordant wild-type mice, intramuscular injection of nickel sulfide induced fibrosarcomas as well (Waalkes *et al.*, 2005). MT-expression, either overexpression (MT-transgenic mice) or no expression (MT-null), did not significantly affect the carcinogenic response to nickel.

(b) Rat

Nickel subsulfide induced lung tumours in rats exposed by intratracheal instillation (Pott *et al.*, 1987). Intrarenal injection resulted in dose-related increases in renal cell tumours, and intraocular injection resulted in eye tumours in rats (Jasmin & Riopelle, 1976; Sunderman *et al.*, 1979; Albert *et al.*, 1982; Sunderman, 1983). Implantation of nickel subsulfide pellets into rat heterotropic tracheal transplant caused carcinomas and sarcomas (Yarita & Nettesheim, 1978). Local tumours were also observed in rats tested by intramuscular and intrarenal injection with nickel disulfide or nickel monosulfide (crystalline but not amorphous form), and in rats tested by intramuscular injection with nickel ferrosulfide matte (Sunderman, 1984; Sunderman *et al.*, 1984).

When administered by intrarenal injection to F344 male rats, nickel subsulfide induced renal sarcomas (Kasprzak *et al.*, 1994), which showed metastases to the lung, liver, and spleen. Injection site tumours (rhabdomyosarcoma,

Table 3.2 Studies of cancer in experimental animals exposed to nickel compounds or nickel powder (inhalation exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel sulfate hexahydrate				
Rat, F344 (M, F) 104 wk Dunnick *et al.* (1995), NTP (1996a)	0, 0.125, 0.25, 0.5 mg/m^3 (equivalent to 0, 0.03, 0.06, 0.11 mg nickel/m^3) for 6 h/d, 5 d/wk 63–65/group/sex	Lung (aveolar/bronchiolar adenomas or carcinomas or squamous cell carcinomas): M–2[a]/54, 0/53, 1/53, 3/53 F[b]–0/52, 0/53, 0/53, 1/54 Adrenal medulla (pheochromocytomas, benign or malignant[c]): M–16/54, 19/53, 13/53, 12/53 F–2/52, 4/52, 3/52, 3/54		Age at start, 6 wk 22.3% Nickel No treatment-related effects on survival. Mean bw of high-dose females were slightly lower than controls. Nickel lung burden values increased with increasing exposure (at 15 mo, 0.15–1.7 µg Ni/g lung)
Mouse, B6C3F$_1$ (M, F) 104 wk Dunnick *et al.* (1995), NTP (1996a)	0, 0.25, 0.5, 1.0 mg/m^3 (equivalent to 0, 0.06, 0.11, 0.22 mg nickel/ m^3) 6 h/d, 5 d/wk 63–65/group/sex	Lung (aveolar/bronchiolar adenomas or carcinomas): M–13/61, 18/61, 7/62, 8/61 F–7/61, 6/60, 10/60, 2/60		Age at start, 6 wk 22.3% Nickel No treatment-related effects on survival. Bw of high-dose males and all exposed female groups were decreased Nickel lung burden (µg Ni/g lung) below limit of detection at 7 and 15 mo interim evaluations

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel subsulfide				
Rat, F344 (M, F) 104 wk Dunnick *et al.* (1995), NTP (1996b)	0, 0.15, 1 mg/m^3 (equivalent to 0, 0.11, 0.73 mg nickel/m^3) 6 h/d, 5 d/wk 63/group/sex	Lung (aveolar/bronchiolar adenomas or carcinomas or squamous cell carcinomas): M–0/53, 6/53, 11/53 F–2/53, [a]6/53, 9/53 Adrenal medulla (pheochromocytomas, benign or malignant): M–14/53, 30/53, 42/53 F–3/53, 7/53, 36/53	M: mid dose $P < 0.05$, high dose $P \leq 0.01$, $P_{trend} < 0.01$ F: mid dose $P \leq 0.05$ vs historical control, high dose $P < 0.05$, $P_{trend} < 0.05$ M: mid dose $P < 0.01$, high dose < 0.001, $P_{trend} < 0.001$ F: high dose, $P < 0.001$ $P_{trend} < 0.001$	Age at start, 6 wk 73.3% Nickel No treatment-related effects on survival. Bw in high-dose groups Nickel lung burden increased with increasing exposure but reached steady-state by 15 mo (4–7 µg Ni/g lung). Lung carcinomas also were significantly increased in high-dose males
Mouse, B6C3F$_1$ (M, F) 104 wk Dunnick *et al.* (1995), NTP 1996b	0, 0.6, 1.2 mg/m^3 (equivalent to 0, 0.44, 0.9 mg nickel/m^3) 6 h/d, 5 d/wk 63/group	Lung (aveolar/bronchiolar adenomas or carcinomas): M–13/61, 5/59, 6/58 F–9/58, 2/59, 3/60	$P = 0.038N^h$ mid dose vs control $P = 0.028N^h$ mid dose vs control $P = 0.050N^h$ high dose vs control	Age at start, 6 wk 73.3% Nickel No treatment-related effects on survival. Mean bw lower in exposed groups than control group. Nickel lung burden increased with exposure concentration and with time (at 15 mo, 12–26 µg Ni/g lung)

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M, F) 78–80 wk + held 30 wk Ottolenghi *et al.* (1975)	Nickel subsulfide with or without 1 mo pre-exposure to the airborne system (clean air or nickel sulfide dust 0.97 ± 0.18 mg/m³ for 5 d/wk), followed by injection of hexachlorotetrafluorobutane to half the animals, thereafter the inhalation exposure was continued for all animals 16 exposure groups (8 groups/sex) Pre-exposure Inj. Controls: 29 (M), 28 (F) Inj. NiS: 29 (M), 28 (F) No Inj. Controls: 28 (M), 30 (F) No Inj. NiS: 22 (M), 26 (F) No Pre-exposure Inj. Controls: 32 (M), 32 (F) Inj. NiS: 24 (M), 32 (F) No Inj. Controls: 31 (M), 31 (F) No Inj. NiS: 32 (M), 26 (F)	Lung (adenomas, adenocarcinomas, squamous cell carcinomas, fibrosarcomas): NiS–17 (M), 12 (F) Controls–1 (M), 1 (F) Adrenal gland (hyperplasias and pheochromocytomas): NiS–12% Controls–1.1%	M, F: $P < 0.01$ $P < 0.01$	Pre-exposure: animals assigned airborne system for 1 mo No pre-exposure: animals housed in normal conditions for 1 mo Inj. = intravenous injection with pulmonary infraction agent Treatment-related decreased survival and decreased bw in males and females starting at 26 wk Inflammatory response – pneumonitis, bronchitis and emphysema Hyperplasias and squamous metaplasic changes in bronchial and bronchiolo-alveolar regions Infraction had no effect on carcinogenicity

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel oxide				
Rat, F344 (M, F) 104 wk Dunnick *et al.* (1995), NTP (1996c)	0, 0.62, 1.25, 2.5 mg/m^3 (equivalent to 0, 0.5, 1.0, 2.0 mg nickel/ m^3) 6 h/d, 5 d/wk 65/group/sex	Lung (aveolar/bronchiolar adenomas or carcinomas, or squamous cell carcinomas): M–1[a]/54, 1/53, 6/53, 4/52 F–1/53, 0/53[d], 6/53, 5/54	M, F: mid dose & high dose, $P \leq 0.05$ vs high dose	Age at start, 6 wk 76.6% Nickel No treatment-related effects on survival or bw Nickel lung burden increased with exposure and with time (at 15 mo, 262–1116 µg Ni/lung)
		Adrenal medulla (pheochromocytomas, benign or malignant): M–27/54, 24/53, 27/53, 35/54 F[e]–4/51, 7/52, 6/53, 18/54	M: high dose, $P = 0.027$, $P_{trend} = 0.008$ F: high dose, $P = 0.01$, $P_{trend} < 0.001$	If the squamous cell carcinomas (lung tumours) are not included, then the mid dose and high dose are significant vs the current controls Significantly increased incidence of malignant pheochromocytomas in high-dose males
Mouse, B6C3F$_1$ (M, F) 104 wk Dunnick *et al.* (1995), NTP (1996b)	0, 1.25, 2.5, 5.0 mg/m^3 (equivalent to 0, 1.0, 2.0, 3.9 mg nickel/m^3) 6 h/d, 5 d/wk ≈80/group/sex	Lung (aveolar/bronchiolar adenomas or carcinomas): M–9/57, 14/67, 15/66, 14/69 F–6/64, 15/66, 12/63, 8/64	F: low dose, $P \leq 0.01$	Age at start, 6 wk; 76.6% Nickel No treatment-related effects on survival or bw Nickel lung burden increased with exposure and with time (at 15 mo, 331–2258 µg Ni/lung)

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel metal powder				
Rat, Wistar Crl:Wi (G1XBRl/Han) (M, F) 12–30 mo Oller *et al.* (2008)	0, 0.1, 0.4, 1 mg/m^3 for 6 h/d, 5 d/wk, exposure time, additional hold time– Group 1: 0, 24 mo, 6 mo Group 2: 0.1, 24 mo, 6 mo Group 3, F: 0.4, 19 mo, 11 mo Group 3, M: 0.4, 24 mo, 6 mo Group 4, F: 1.0, ~14 mo, 0 mo Group 4, M: 1.0, ~12 mo, 0 mo 50/group	Groups 1, 2, 3 Adrenal gland (pheochromocytomas, benign or malignant): M–0/50, 5/50, 21/50 F–0/50, 5/49, 3/53 Adrenal cortex (adenomas or carcinomas): M–1/50, 3/50, 2/50 F–2/50, 2/49, 7/54	M: 0.4 mg/m^3 Significant increase for benign, malignant, benign combined, significant dose-related response[f] F: 0.4 mg/m^3 Significant increase for combined (adenoma and carcinoma) and significant dose-related response[f]	Age at start, 6 wk 99.9% pure Exposure-related mortality was observed in the high-dose group (Group 4 M, F, these animals were removed from the main study), and in Group 3 F (animals from satellite study reassigned to main study). Exposure-related bw effects were observed in Groups 2 (M), 3 (F &M), and 4 (F &M). Exposure-related lung toxicity was observed. Nickel lung burden (µg Ni/lung) increased with exposure and with time (appeared to reach steady-state at 12 mo)[g]. Increases in adrenal tumours were within published (external) historical controls for Wistar rats

[a] Includes 1 squamous cell carcinoma
[b] Only alveolar bronchiolar adenomas observed in female rats; adjusted rate not reported
[c] Adjusted rates not provided
[d] Dunnick reported 1 tumour and NTP technical report reported 0
[e] Only benign tumours observed.
[f] *P*-value not reported calculated by Peto
[g] Data not available for all time points
[h] A negative trend or a lower incidence in an exposure group is indicated by N
bw, body weight; d, day or days; h, hour or hours; F, female; M male; mo, month or months; Ni, nickel; NR, not reported; vs, versus; wk, week or weeks

fibromas, malignant fibrous histiocytomas or leiomyosarcomas) were observed in male or female F344 rats administered nickel subsulfide intramuscularly (Ohmori *et al.*, 1990; Kasprzak & Ward, 1991), and intra-articularly (Ohmori *et al.*, 1990). One study found that in female rats subjected to bone fractures and treated intramuscularly or intra-articularly had a shorter time to sarcoma formation, reduced survival time, and higher metastatic rate than rats treated with nickel alone (Ohmori *et al.*, 1990). Ohmori *et al.* (1999) studied strain susceptibility in male and female Wistar rats, and one strain (CRW) was found to be more sensitive to intramuscular injection of nickel.

(c) Hamster

Nickel subsulfide induced local sarcomas after repository injections at multiple sites in numerous studies in hamsters (IARC, 1990).

(d) Rabbit

Nickel subsulfide induced local sarcomas after repository injections at multiple sites in numerous studies rabbits (IARC, 1990).

3.3.2 Nickel oxide and hydroxide

Nickel oxide induced lung tumours in rats by intratracheal instillation (Pott *et al.*, 1987), local sarcomas in mice by intramuscular injection (Gilman, 1962), and rats by intramuscular, intrapleural, and intraperitoneal injection (Gilman, 1962; Sunderman & McCully, 1983; Skaug *et al.*, 1985; Pott *et al.*, 1987). Nickel hydroxide induced local sarcomas in rats when tested by intramuscular injection (Gilman, 1966; Kasprzak *et al.*, 1983).

Sunderman *et al.* (1990) tested the carcinogenicity of five nickel oxides or nickel-copper oxides in male Fisher 344 rats. The three oxides that induced sarcomas at the injection sites had measurable dissolution rates in body fluids, and were strongly positive in an erythrocytosis stimulation assay, demonstrating nickel bioavailability.

3.3.3 Nickel acetate

(a) Mouse

Nickel acetate when administered by intraperitoneal injection induced lung adenocarcinomas and pulmonary adenomas in Strain A mice (Stoner *et al.*, 1976; Poirier *et al.*, 1984).

(b) Rat

Nickel acetate induced malignant tumours in the peritoneal cavity when administered by intraperitoneal injection in rats (Pott *et al.*, 1989, 1990).

A single intraperitoneal injection of nickel acetate initiated renal epithelial tumours (including carcinoma) after promotion using sodium barbital in the drinking-water in male rats (Kasprzak *et al.*, 1990).

See Table 3.3.

3.3.4 Metallic nickel

Intratracheal administration of metallic nickel powder caused lung tumours in rats (Pott *et al.*, 1987). Metallic nickel also caused local tumours in rats when administered by injection (intrapleural, subcutaneous, intramuscular, and intraperitoneal) (Hueper, 1952, 1955; Mitchell *et al.*, 1960; Heath & Daniel, 1964; Furst & Schlauder, 1971; Berry *et al.*, 1984; Sunderman, 1984; Judde *et al.*, 1987; Pott *et al.*, 1987, 1990).

3.3.5 Nickel sulfate

Nickel sulfate induced malignant tumours in the peritoneal cavity when administered by intraperitoneal injection in rats (Pott *et al.*, 1989, 1990).

Table 3.3 Studies of cancer in experimental animals exposed to nickel compounds (parenteral administration and intratracheal instillation)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel subsulfide				
Mouse, Strain A (M) 45 wk McNeill *et al.* (1990)	i.t. and i.p. 0, 0.53, 0.160 mg/kg bw 3 dosing regimens for 15 wk 1/wk (15 treatments), 1 every 2 wk (8 treatments), 1 every 3 wk (5 treatments); 3 doses per regiment; 30/group 10 mice sacrified after 20 wk	Lung (adenomas at 45 wk[a]): i.t.– Number of treatments: dose 5: 68%, 63%, 58% 8: 64%, 54%, 61% 15: 47%, 47%, 56% i.p.– 5: 68%, 63%, 53% 8: 58%, 53%, 63% 15: 63%, 47%, 50%		Age at start, 8–10 wk Nickel subsulfide –1.8 µm mass medium diameter 73% Nickel and 26.3% sulfur (weight) Urethane (positive control) significantly increased tumour incidence i.p., i.t., after 20 wk, and i.t. after 45 wk, average. number of adenoma/mouse increased i.p. and i.t. at both time points No treatment effects on bw
Mouse, C57BL/6, $B6C3F_1$, CeH/He (M) 78 wk Rodriguez *et al.* (1996)	i.m. (thigh) 0, 0.5, 1.0, 2.5, 5.0, 10 mg/site (single injection) 30/group	Injection site (rhabdomyosarcomas, fibrosarcomas, and other e.g. liposarcomas, haemangiosarcomas): C3He 0/30, 5/30 (16.6%), 10/30 (33.3%), 20/27 (74.1%), 28/29, (96.6%) 14/14 (100%) $B6C3F_1$ 0/30, 2/29 (6.9%), 8/30 (26.7%), 15/30 (50.0%), 16/20 (80%), 5/6 (83.3%) C57BL 0/24, 1/27 (3,7%), 4/28 (14.3%), 6/21 (28.6%), 6/15(40%), 0/2	[$P = 0.052$, 0.5 mg; $P < 0.001$ for other doses][a] [$P < 0.01$, 1.0 mg, $P < 0.001$, 2.5, 5.0, 10 mg][a] [$P < 0.01$, 2.5, 5 mg][a]	Age at start, 6–8 wk; weight, 23–29 g High dose was lethal within 1 wk to over 50% of all 3 strains; susceptibility was C57BL > B6C3F1 > C3H Treatment-related decrease in bw was observed for C3H and $B6C3F_1$ at 2 highest doses. Tumours of the liver, lung adenomas and leukaemias were also observed, but were not increased in exposed groups compared to controls Susceptibility to tumours C3H > $B6C3F_1$ > C57BL

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, MT transgenic and wild-type (M) 104 wk Waalkes *et al.* (2004)	i.m. (both thighs) 0, 0.5, 1 mg/site (single injection) 25/group	Injection site (primarily fibrosarcomas, but also included fibromas and lymphosarcomas): WT–0/24, 5/25 (20%), 10/25 (40%) MT-Tg–0/25, 7/25 (28%), 7/24 (29%) Lung (adenomas or adenocarcinomas): WT–6/24 (25%), 5/25 (20%), 9/25 (36%) MT-Tg–0/25, 3/25 (12%), 4/24 (17%)	WT: $P < 0.05$, mid-and low dose, $P_{trend} < 0.0001$ MT-Tg: $P < 0.05$, mid-and low dose, $P_{trend} = 0.0081$ trend MT-Tg: $P = 0.0502$ high dose $P_{trend} = 0.046$	Age at start, 12 wk 99.9% pure, 30 µm particles Average survival time less in MT-Tg mice than controls. Treatment-related decrease in survival in WT but not MT-Tg mice. No effect on bw No differences in injection-site tumour incidence or latency between MT-Tg and WT mice MT-transgenic controls had significantly lower incidence of lung tumours than WT controls.
Mouse, MT-null (double knockout) and wild-type (M) 104 wk Waalkes *et al.* (2005)	i.m. (both thighs) 0, 0.5, 1 mg/site (single injection), 25/group	Injection site (primarily fibrosarcomas, but also included fibromas): WT–0/24, 8/25(32.0%), 18/25 (72.0%) MT-null–0/24, 11/24 (45.8%), 15/23 (62.5%) Lung (adenomas or adenocarcinomas): WT–7/24 (29.2%), 12/25 (48.0%), 11/25 (44.0%) MT-null–10/24 (41.7%), 13/24 (54.2%), 4/23 (16.7%)	$P < 0.05$ low and high dose $P < 0.05$ low and high dose	Age at start, 12 wk 99.9% pure, < 30 µm particles No difference in survival between control MT-null mice and control WT mice. Nickel treatment reduced survival at later time points corresponding to the appearance of sarcomas. Nickel treatment reduced bw in high-and mid dose MT-null and high-dose WT mice

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, MT-null (double knockout) and wild-type (M) 104 wk Waalkes *et al.* (2005) (contd.)		Lung (adenocarcinomas): WT–1/24 (4.2%), 10/25 (40.0%), 3/25 (12.0%) MT-null–3/24 (12.5%), 3/24 (12.5%), 4/23 (17.4%) Lung (adenomas): WT–6/24 (25%), 2/25 (8.0%), 8/25 (32.0%) MT-null–7/24 (29.2%), 10/24 (41.7%), 0/23	WT: $P < 0.05$ low dose MT-null: $P < 0.05$ control vs high dose	
Rat, F344/NCr (M) 109 wk Kasprzak *et al.* (1994)	i.r. (2 injections) Ni_3S_2 – 5 mg, MgCarb –6.2 mg, Fe^0–3.4 mg Groups: treatment, number of animals Group 1: Ni_3S_2, 40 Group 2: Ni_3S_2 + MgCarb, 20 Group 3: MgCarb, 20 Group 4: Ni_3S_2 + Fe^0, 20 Group 5: Fe^0, 20 Group 6: vehicle, 20 20–40/group	Kidney (malignant tumours of mesenchymal cell origin) at 104 wk: Group 1: 25/40 (63%) Group 2: 4/20 (20%) Group 3: 0/20 Group 4: 12/20 (60%) Group 5: 0/20 Group 6: 0/20	Group 2 vs Group 1 [$P < 0.01$][a]	Ni_3S_2 < 10µm No effect on bw or survival (from causes other than kidney tumours) MgCarb also delayed onset of tumours (besides decreasing the incidence), and Fe decreased time until first tumour Metastases to lung, liver, spleen and other kidney

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344/NCr (M) 109 wk Kasprzak & Ward (1991)	i.m. and s.c (single injection) Ni_3S_2– 2.5 mg, MB – 0.5 mg, CORT–1.0 mg, IND –1.0 mg. Groups: i.m., s.c., number of animals Group 1: Ni_3S_2, none, 20 Group 2: MB, none, 20 Group 3: Ni_3S_2+ MB, none, 20 Group 4: CORT, none, 20 Group 5: Ni_3S_2+ CORT, none, 20 Group 6: IND, none, 20 Group 7: Ni_3S_2+ IND, none, 20 Group 8: water, none, 20 Group 9: Ni_3S_2, MB, 20 Group 10: Ni_3S_2, IND, 20 20/group	Injection-site tumours (rhabdomosarcomas, fibrosarcomas, histolytic sarcomas): 36 wk; 71 wk Group 1: 10/20 (50%); 17/20 (85%) Group 2: 0/20; 0/20 Group 3:0/20; 1/20 (5%) Group 4: 0/20; 0/20 Group 5: 9/20 (45%); 17/20 (85%) Group 6: 0/20; 0/20 Group 7: 6/20 (30%); 16/20 (80%) Group 8: 0/20; 0/20 Group 9: 18/20 (90%); 20/20 (100%) Group 10: 13/20 (65%); 19/20 (95%)	[Groups 2, 3, 4, 6 or 8 vs Group 1, 36 & 71 wk, $P < 0.01$; Group 9 vs Group 1, 36 wk, $P < 0.05$][a]	Age at start, 8 wk Ni_3S_2 < 10µm No effect on bw Metastases to the lung MB given away from the injection site (s.c.) decreased tumour latency induced by Ni_3S

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (F) 1 yr Ohmori *et al.* (1990)	Ni_3S_2–10 mg Groups, treatment, number of animals Group 1: fracture bone, 10 mg/fracture, 20 Group 2: 10 mg i.m right thigh, 20 Group 3: 10 mg i.a. right knee joint, 20 Group 4: control (CM), 3 fractured bone, 3 i.m., 2 i.a. 20/group	Injection site (malignant fibrous histiocytomas, rhabdomyosarcomas, fibrosarcomas, leiomyosarcomas): Group 1: 17/20 (85%) Group 2: 20/20 (100%) Group 3: 16/20 (80%) Group 4: 0/7 (0%) Metastasis (lymph node, lung): Group 1: 16/17 (94.1), 9/17 (52.9) Group 2: 5/20 (25.0%), 3/20 (15.0%) Group 3: 3/16 (18.8%), 2/16 (12.5%) Group 4: 0/7, 0/7	$P < 0.05$, Group 1 vs Group 2 or Group 3	Age at start, 10 wk Ni_3S_2 medium particle diameter < 2µm Vehicle, CM Tumour-induction time and survival time shorter in Group 1 than Groups 2 or 3. No osteogenic sarcoma developed in bone-fracture group
Rat, Wistar (M, F) 70 wk Ohmori *et al.* (1999)	Ni_3S_2–10 mg i.m. (single injection) Groups, strain, treatment; number of animals Group 1: SHR–10 mg; 15F, 15M Group 2: CWR–10 mg; 15F, 16M Group 3: SHR–0 mg; 6F, 6M Group 4: CWR–0 mg 7F, 7M 6–15/group	Sarcomas (rhabdomyosarcomas, leiomyosarcomas, fibrosarcomas and malignant fibrous histiocytomas): Groups: F; M; Total Group 1: 2/15 (13.3%); 5/15 (33.3%); 7/30 (23.3%) Group 2: 8/15 (53.3%), 13/16 (81.4%); 21/31 (67.7%) Group 3: 0/6, 0/6 Group 4: 0/7, 0/7	Total: Group 1 vs Group 2, $P < 0.005$	Age, 10 wk Ni_3S_2 medium particle diameter < 2µm Vehicle, CM Tumour incidence, progression (as shown by tumour size and metastasis) was significantly lower in SHR rats (M, F combined) than in CWR rats Metastases observed in the lung and lymph node

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel oxide				
Rat, F344 (M) 104 wk Sunderman *et al.* (1990)	i.m. (hind limb) single injection Group: Ni by wt.; other elements V: vehicle control (glycerol) A: 0.81% Ni (III); none B: 0.05% Ni (III); none F: < 0.03% Ni (III); none H: 21% Cu, 2% Fe, 1.1% Co, 1% S, 0.5% Ni_3S_2 I: 13% Cu, 1.2% Fe, 1.0 Co, 0.3% S, 1.0% Ni_3S_2 (positive control) 20 mg Ni/rat 15/group	Injection site (rhabdomyosarcomas, fibrosarcomas, malignant fibrous histiocytomas, leiomyosarcomas, undifferentiated): V, 0/15; A, 6/15 (40.0%); B, 0/15; F, 0/15; H, 13/15 (86.7%); I, 15/15 (100%) Positive control, Ni_3S_2 15/15(100%) **Metastases** V: 0, A: 3; B: 0; F: 0; H: 4; I: 4 Ni_3S_2: 12 **Other primary tumours** V: 0; A: 0; B: 3; F: 0; H: 0; I: 3 Ni_3S_2: 0	$P < 0.01$ A; $P < 0.001$ H, I, Ni_3S_2	Age at start, ~2 mo 5 NiO compounds – all compounds had 52–79% Nickel (total), and 22–24% O. Nickel could not be determined in Groups H and I because of the presence of sulfur Groups A, H, and I all had measurable dissolution rates in body fluids and were strongly positive in an erythrocytosis-stimulation assay Compounds B and F were insoluble in body fluids, did not stimulate erythrocytosis and had little Ni (III), Cu Fe, Co, or S
Rat, Wistar (F) Life span Pott *et al.* (1987)	(mg x wk) number of animals NiO 50 mg (10 × 5); 34 150 mg (10 × 15); 37 Ni_3S_2 0.94 mg (15 × 0.063); 47 1.88 mg (15 × 0.125); 45 3.75 mg (15 × 0.25); 47 Nickel powder 6 mg (20 × 0.3); 32 9 mg (10 × 0.9); 32 32–47/group	Lung (adenomas, adenocarcinomas, squamous cell carcinomas): % tumours for each dose NiO–27%, 31.6% Ni_3S_2–15%, 28.9% Nickel powder–25.6%, 25% Saline, 0%		Age at start, 11 wk NiO, 99.9% pure

Table 3.3 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Nickel acetate				
Rat, F344/NCr (M) 101 wk Kasprzak *et al.* (1990)	NiAcet –90 µmol/kg bw single i.p. injection NaBB–50 ppm in drinking-water (2 wk after NiAcet) Groups, treatment, # of animals Group 1: NiAcet, 23 Group 2: NiAcet + NaBB, 24 Group 3: NaBB, 24 Group 4: Saline, 24 24/group	Renal cortical tumours (adenomas & adenocarcinomas): Group 1–1/23 (4.3%) Group 2–16/24 (66.7%) (4 carcinomas) Group 3–6/24 (25%) Group 4–0/24 Renal pelvic tumours (papillomas & carcinomas): Group 1–0/23 Group 2–8/24 (33.3%) Group 3–13/24 (54.2%) (1 carcinoma) Group 4–0/24	$P < 0.008$ vs Group 3	Age at start, 5 wk Initiation/promotion study Decreased survival and bw in rats given nickel acetate followed by NaBB Kidney weight increased in Groups 2 and 3 Renal cortical tumours: metastatic nodules observed in the lung, spleen and liver
Mouse, Strain A (M, F) 30 wk Stoner *et al.* (1976)	i.p. Nickel acetate 3×/wk (24 injections total) 0, 72, 180, 360 mg/kg Saline control 20/group	Lung (adenomas): Average number of tumours/mouse (mean ± SD) Saline: 0.42 ± 0.10 72: 0.67 ± 0.16 180: 0.71 ± 0.19 360: 1.26 ± 0.29	$P < 0.01$ high dose	Age at start, 6–8 wk 99.9% pure Sample of nodules confirmed by histopathology No difference in control M, F, so M, F were combined Positive control urethane Control saline Doses correspond to MTD, ½ MTD, 1/5 MTD
Mouse, Strain A (M, F) 30 wk Poirier *et al.* (1984)	i.p. Nickel acetate 10.7 mg/kg bw (0.04 mmol kg/bw)/injection 3×/wk (24 injections total) 30/group/sex	Lung (adenomas): Average number of tumours/mouse (mean ± SD) Saline: 0.32 ± 0.12 Nickel acetate: 1.50 ± 0.46	$P < 0.05$	Age at start, 6–8 wk Nodules (sample) confirmed by histology Co-exposure to calcium and magnesium decreased multiplicity

[a] Calculated by Fisher Exact Test, Significance not reported by authors

bw, body weight; CM, chloromycetin; CORT, cortisol; CWR, common closed colony rats; F, female; Fe^0, metallic iron; HSR, spontaneously hypertensive rats; i.a., intra-articular; i.f., intra-fat; i.m., intramuscular; IND, indometacin; i.p., intraperitoneal; i.r., intrarenal; i.t., intratracheal instillation; M, male; MB, *Mycobacterium bovis* antigen; MgCarb, magnesium basic carbonate; MT, metallothionien; MTD, maximum tolerated dose; NABB, sodium barbital; Ni, nickel; NiAcet, nickel acetate; Ni_3S, nickel subsulfide; s.c., subcutaneous; SD, standard deviation; Tg, Transgenic; wk, week or weeks; WT, wild type; yr, year or years

Table 3.4 Studies of cancer in experimental animals exposed to nickel acetate (transplacental exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Results Target organs	Significance	Comments
Rat, F344/NCr (M, F) 85 wk Diwan *et al.* (1992)	*Dams – i.p* NiAcet (90 µmol/kg wt total) Group:/µmol/kg bw; regimen Group 1: 90; once at Day 17 of gestation Group 2: 45; twice at Days 16 & 18 of gestation Group 3: 45; 4 times at Days 12, 14, 16, 18 of gestation Group 4: control (180 NaAcet) once at Day 18 of gestation *Offspring 4 to 85 wk (drinking-water)* ad libitum 1A, 2A, 4A – tap water 1B, 2B, 4B – 0.05% NBB	Renal tumours (cortex adenomas and carcinomas; or pelvis papillomas and carcinomas): 1A: 0/17 (M), 0/16 (F) 2A: 0/15 (M), 0/15 (F) 4A: 0/15 (M), 0/16 (F) 1B: 8/15 (53.3%, M), 0/15 (F) 2B: 7/15 (46.7%, M), 0/15 (F) 4B: 1/15 (6.67%, M), 0/14 (F) Pituitary gland (adenomas or carcinomas): 1A: 9/17 (52.9%, M), 5/16 (31.3%, F), 14/33 (42.3%, M, F) 2A: 6/15 (40.0%, M), 8/16 (50%, F), 14/31 (45.2%, M, F) 4A: 1/15 (6.7%, M), 3/14 (21.4%, F) 1B: 6/15 (40.0%, M), 5/15 (33.3%, F) 2B: 7/15 (46.7%, M), 6/15 (40.0%, F) 4B: 2/15 (13.3%, M), 4/14 (28.6%, F)	M: $P = 0.007$ (1B vs 4B) M: $P = 0.012$ (2B vs 4B) M, F: $P = 0.12$ 1A vs 4A M, F: $P = 0.008$ 2A vs 4A	Dams, age at start 3–4 mo Purity not provided Male (Groups 1 & 2) – significantly decreased bw at 75 wk All offspring in Group 3 died at 72 h. Survival was decreased in Groups 1A, 1B, 2A and 2B compared to controls (4A and 4B) Pituitary tumours: significantly decreased latency for Groups 1A (M, F), 1B (M, F) and 2A (F) compared to the Groups 4A or 4B (corresponding M or F)

h, hour or hours; F, female; i.p., intraperitoneal; M, male; mo, month or months; NaBB, sodium barbital; vs, versus; wk, week or weeks

3.3.6 Nickel chloride

Nickel chloride induced malignant tumours in the peritoneal cavity when administered by intraperitoneal injection in rats (Pott *et al.*, 1989, 1990).

3.3.7 Other forms of nickel

Intramuscular administration of nickel sulfarsenide, nickel arsenides, nickel antimonide, nickel telluride, and nickel selenides caused local sarcomas in rats (Sunderman & McCully, 1983). Intramuscular administration of nickelocene caused some local tumours in rats and hamsters (Furst & Schlauder, 1971).

3.4 Transplacental exposure

3.4.1 Nickel acetate

Diwan *et al.* (1992) studied the carcinogenic effects of rats exposed transplacentally to nickel acetate and postnatally to sodium barbital in drinking-water. Pregnant F344 were given nickel acetate by intraperitoneal injection, and their offspring were divided into groups receiving either tap water or sodium barbital in drinking-water. An increased incidence in pituitary tumours was observed in the offspring of both sexes transplacentally exposed to nickel acetate. These tumours were mainly malignant, and are rare tumours. Renal tumours were observed in the male offspring exposed transplacentally to nickel acetate, and receiving sodium barbital postnatally, but not in the male offspring receiving tap water after nickel *in utero*.

See Table 3.4.

3.5 Synthesis

The inhalation of nickel oxide, nickel subsulfide, and nickel carbonyl caused lung tumours in rats. Intratracheal instillation of nickel oxide, nickel subsulfide, and metallic nickel caused lung tumours in rats. Lung tumours were observed by the intraperitoneal injection of nickel acetate in two studies in A/J mice, and by intramuscular injection of nickel subsulfide in mice. The inhalation of nickel oxide, nickel subsulfide, and metallic nickel caused adrenal medulla pheochomocytoma in rats. Transplacental nickel acetate induced malignant pituitary tumours in the offspring in rats. Several nickel compounds (nickel oxides, nickel sulfides, including nickel subsulfide, nickel sulfate, nickel chloride, nickel acetate, nickel sulfarsenide, nickel arsenide, nickel antimonide, nickel telluride, nickel selenide, nickelocene, and metallic nickel) administered by repository injection caused sarcomas in multiple studies. The inhalation of metallic nickel did not cause lung tumours in rats. The inhalation and oral exposure to nickel sulfate did not cause tumours in rats or mice. The inhalation of nickel subsulfite did not cause tumours in mice.

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

In rodents, nickel salts and nickel sulfides are absorbed through the lungs and excreted mainly in the urine (Benson *et al.*, 1994, 1995a). After inhalation exposure to green nickel oxide, nickel is not distributed in extrapulmonary tissues, and is excreted only in faeces (Benson *et al.*, 1994). In humans, soluble nickel compounds are rapidly absorbed through the lungs, and excreted in the urine. After inhalation exposure to insoluble nickel species, elevated concentrations of nickel are observed in the plasma and urine, but the absorption is slow (Bernacki *et al.*, 1978; Tola *et al.*, 1979).

In rats exposed to nickel sulfate hexahydrate by inhalation for 6 months or 2 years,

no pulmonary accumulation is observed; in a similar exposure scenario with nickel subsulfide, concentrations of nickel are detected in the lungs, with very slight nickel accumulation. Following the exposure of green nickel oxide to rats, the nickel lung clearance half-life is approximately 130 days, and in long-term exposure (NTP, 1996a, b, c; described in Section 3), a remarkable accumulation of nickel is observed (Benson *et al.*, 1995b; Dunnick *et al.*, 1995). The lung clearance half-life of nanoparticulate black nickel oxide in rats is reported as 62 days (Oyabu *et al.*, 2007). The difference in the two clearance rates may be related to the greater water solubility (and the smaller particle size) of the nanoparticulate black nickel oxide. In mice, the observed clearance for nickel sulfate is fast, but for nickel subsulfide intermediate and for green nickel oxide, very slow (Dunnick *et al.*, 1995).

4.1.1 Cellular uptake

Nickel chloride has been shown in different cell lines in culture to be transported to the nucleus (Abbracchio *et al.*, 1982; Edwards *et al.*, 1998; Ke *et al.*, 2006, 2007; Schwerdtle & Hartwig, 2006). Soluble nickel chloride compounds enter cells via the calcium channels and by metal ion transporter 1 (Refsvik & Andreassen, 1995; Funakoshi *et al.*, 1997; Gunshin *et al.*, 1997; Garrick *et al.*, 2006). Crystalline nickel sulfides are phagocytized by a large variety of different cells in culture (Kuehn *et al.*, 1982; Miura *et al.*, 1989; Hildebrand *et al.*, 1990, 1991; IARC, 1990).

Black nickel oxide and nickel chloride are taken up by human lung carcinoma cell lines A549 in culture; the nucleus/cytoplasm ratio is > 0.5 for black nickel oxide, and < 0.18 for nickel chloride (Fletcher *et al.*, 1994; Schwerdtle & Hartwig, 2006).

After phagocytosis of nickel subsulfide, intracellular nickel containing particles rapidly dissolve, and lose sulfur (Arrouijal *et al.*, 1990; Hildebrand *et al.*, 1990, 1991; Shirali *et al.*, 1991).

4.2 Genetic and related effects

The mechanisms of the carcinogenicity of nickel compounds have been reviewed extensively (Hartwig *et al.*, 2002; Zoroddu *et al.*, 2002; Costa *et al.*, 2003, 2005; Harris & Shi, 2003; Kasprzak *et al.*, 2003; Lu *et al.*, 2005; Durham & Snow, 2006; Beyersmann & Hartwig, 2008; Salnikow & Zhitkovich, 2008).

Based on the uptake and distribution in cells described above, the ultimate genotoxic agent is Ni (II). However, direct reaction of Ni (II) with DNA does not seem to be relevant under realistic exposure conditions. Nevertheless, nickel is a redox-active metal that may, in principle, catalyse Fenton-type reactions, and thus generate reactive oxygen species (Nackerdien *et al.*, 1991; Kawanishi *et al.*, 2001). Genotoxic effects have been consistently observed in exposed humans, in experimental animals, and in cell culture systems, and include oxidative DNA damage, chromosomal damage, and weak mutagenicity in mammalian cells. These effects are likely to be due to indirect mechanisms, as described in detail below.

4.2.1 Direct genotoxicity

(a) DNA damage

Water-soluble as well as water-insoluble nickel compounds induce DNA strand breaks and DNA protein crosslinks in different mammalian test systems, including human lymphocytes. Nevertheless, in the case of DNA strand breaks and oxidative DNA lesions, these events mainly occur with conditions that involve comparatively high cytotoxic concentrations (IARC, 1990; Pool-Zobel *et al.*, 1994; Dally & Hartwig, 1997; Cai & Zhuang, 1999; Chen *et al.*, 2003; M'Bemba-Meka *et al.*, 2005; Schwerdtle & Hartwig, 2006; Caicedo *et al.*, 2007). This is also true for the induction of oxidative DNA base modifications in cellular systems. Nevertheless, oxidative DNA damage is also observed in experimental animals, this may

be due to repair inhibition of endogenous oxidative DNA damage.

The intratracheal instillation of several soluble and insoluble nickel compounds to rats significantly increases 8-hydroxydeoxyguanine (8-OH-dG) content in the lungs. Concomitantly, microscopic signs of inflammation in the lungs are also observed. Two distinct mechanisms are proposed: one via an inflammatory reaction and the other through cell-mediated reactive oxygen species formation (Kawanishi *et al.*, 2001; Kawanishi *et al.*, 2002).

(b) Chromosomal alterations

Water-soluble and poorly water-soluble nickel compounds induce sister chromatid exchange and chromosomal aberrations at toxic levels in different mammalian test systems (Conway *et al.*, 1987; Conway & Costa, 1989; IARC, 1990; Howard *et al.*, 1991). Chromosomal aberrations are most pronounced in heterochromatic chromosomal regions (Conway *et al.*, 1987). Water-soluble and poorly water-soluble nickel compounds induce micronuclei at comparatively high concentrations. Because increases in both kinetochore-positive and -negative micronuclei are observed, these effects are likely due to aneugenic as well as clastogenic actions (Arrouijal *et al.*, 1990, 1992; Hong *et al.*, 1997; Seoane & Dulout, 2001). The induction of chromosomal aberrations and micronuclei in rodents treated with different nickel compounds is not consistent across studies (Sobti & Gill, 1989; Arrouijal *et al.*, 1990; Dhir *et al.*, 1991; IARC, 1990; Oller & Erexson, 2007). Enhanced frequencies of chromosomal aberrations were observed in some studies in lymphocytes of nickel-exposed workers (IARC, 1990).

(c) Gene mutations in bacterial and mammalian test systems

Nickel compounds are not mutagenic in bacterial test systems, and are only weakly mutagenic in cultured mammalian cells. Even though, mutagenic responses for both water-soluble and water-insoluble nickel compounds have been reported in transgenic G12 cells, this effect was later shown to result from epigenetic gene-silencing (Lee *et al.*, 1995). Nevertheless, the prolonged culture of V79 cells after treatment with nickel sulfate results in the appearance of genetically unstable clones with high mutation rates together with chromosomal instability (Little *et al.*, 1988; Ohshima, 2003).

(d) Cell transformation

Water-soluble and poorly water-soluble nickel compounds induced anchorage-independent growth in different cell systems (IARC, 1990), including the mouse-embryo fibroblast cell-line PW and the human osteoblast cell line HOS-TE85 (Zhang *et al.*, 2003). Nickel compounds were shown to cause morphological transformation in different cell types (Conway & Costa, 1989; Miura *et al.*, 1989; Patierno *et al.*, 1993; Lin & Costa, 1994).

4.2.2 Indirect effects related to genotoxicity

As stated above, the direct interaction of nickel compounds with DNA appears to be of minor importance for inducing a carcinogenic response. However, several indirect mechanisms have been identified, which are discussed below.

(a) Oxidative stress

Treatment with soluble and insoluble nickel causes increases in reactive oxygen species in many cell types (Huang *et al.*, 1993; Salnikow *et al.*, 2000; Chen *et al.*, 2003).

Increased DNA stand breaks, DNA–protein crosslinks and sister chromatid exchange are found in cells treated with soluble and insoluble nickel compounds, and these are shown to result from the increase in reactive oxygen species (Chakrabarti *et al.*, 2001; Błasiak *et al.*, 2002; Woźniak & Błasiak, 2002; M'Bemba-Meka *et al.*, 2005, 2007).

Intraperitoneal injection of nickel acetate in rat did not cause any DNA damage in liver and kidney at 12 hours. However, oxidative DNA damage increased after 24 hours, and persisted in the kidney for 14 days (Kasprzak *et al.*, 1997).

(b) Inhibition of DNA repair

The treatment of cells with soluble Ni (II) increases the DNA damage and the mutagenicity of various agents (Hartwig & Beyersmann, 1989; Snyder *et al.*, 1989; Lee-Chen *et al.*, 1993).

Soluble Ni (II) inhibits nucleotide-excision repair after UV irradiation, and the effect seems to be on the incision, the polymerization, and ligation steps in this pathway (Hartwig *et al.*, 1994; Hartmann & Hartwig, 1998; Woźniak & Błasiak, 2004). One of the proteins in nucleotide-excision repair, the XPA protein, may be a target of Ni (II) (Asmuss *et al.*, 2000a, b).

Soluble nickel chloride also inhibits base-excision repair. The base-excision repair enzyme, 3-methyladenine-DNA glycosylase II, is inhibited specifically (Dally & Hartwig, 1997; Woźniak & Błasiak, 2004; Wang *et al.*, 2006).

There is some evidence that the enzyme O^6-methylguanine-DNA methyltransferase (MGMT) is inhibited by nickel chloride (Iwitzki *et al.*, 1998).

(c) Epigenetic mechanisms

Both water-soluble and water-insoluble nickel compounds are able to cause gene silencing (Costa *et al.*, 2005). This effect was first found when "mutations" in the transgenic *gpt* gene in G12 cells were found to be epigenetically silenced rather than mutated (Lee *et al.*, 1995). Genes that are located near heterochromatin are subject to such inactivation by nickel. The *gpt* gene was silenced by DNA methylation. Additional studies show that cells treated with nickel have decreased histone acetylation, and altered histone methylation patterns (Golebiowski & Kasprzak, 2005; Chen *et al.*, 2006). Nickel also causes ubiquination and phosphorylation of histones (Karaczyn *et al.*, 2006; Ke *et al.*, 2008a, b). Permanent changes in gene expression are important in any mechanism of carcinogenesis.

4.3 Synthesis

The ultimate carcinogenic species in nickel carcinogenesis is the nickel ion Ni (II). Both water-soluble and poorly water-soluble nickel species are taken up by cells, the former by ion channels and transporters, the latter by phagocytosis. In the case of particulate compounds, nickel ions are gradually released after phagocytosis. Both water-soluble and -insoluble nickel compounds result in an increase in nickel ions in the cytoplasm and the nucleus. Nickel compounds are not mutagenic in bacteria, and only weakly mutagenic in mammalian cells under standard test procedures, but can induce DNA damage, chromosomal aberrations, and micronuclei *in vitro* and *in vivo*. However, delayed mutagenecity and chromosomal instability are observed a long time after treatment of cells with nickel. Nickel compounds act as co-mutagens with a variety of DNA-damaging agents. Thus, disturbances of DNA repair appear to be important. A further important mechanism is the occurrence of epigenetic changes, mediated by altered DNA methylation patterns, and histone modification. Inflammation may also contribute to nickel-induced carcinogenesis.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of mixtures that include nickel compounds and nickel metal. These agents cause cancers of the lung and of the nasal cavity and paranasal sinuses.

There is *sufficient evidence* in experimental animals for the carcinogenicity of nickel monoxides, nickel hydroxides, nickel sulfides (including

nickel subsulfide), nickel acetate, and nickel metal.

There is *limited evidence* in experimental animals for the carcinogenicity of nickelocene, nickel carbonyl, nickel sulfate, nickel chloride, nickel arsenides, nickel antimonide, nickel selenides, nickel sulfarsenide, and nickel telluride.

There is *inadequate evidence* in experimental animals for the carcinogenicity of nickel titanate, nickel trioxide, and amorphous nickel sulfide.

In view of the overall findings in animals, there is *sufficient evidence* in experimental animals for the carcinogenicity of nickel compounds and nickel metal.

Nickel compounds are *carcinogenic to humans (Group 1).*

References

Abbracchio MP, Simmons-Hansen J, Costa M (1982). Cytoplasmic dissolution of phagocytized crystalline nickel sulfide particles: a prerequisite for nuclear uptake of nickel. *J Toxicol Environ Health*, 9: 663–676. doi:10.1080/15287398209530194 PMID:7108981

Albert DM, Gonder JR, Papale J *et al.* (1982). *Induction of ocular neoplasms in Fischer rats by intraocular injection of nickel subsulfide.* In: *Nickel Toxicology.* London: Academic Press, pp. 55–58.

Andersen A, Berge SR, Engeland A, Norseth T (1996). Exposure to nickel compounds and smoking in relation to incidence of lung and nasal cancer among nickel refinery workers. *Occup Environ Med*, 53: 708–713. doi:10.1136/oem.53.10.708 PMID:8943837

Antonsen DH, Meshri DT (2005). *Nickel compounds.* In: *Kirk-Othmer Encyclopedia of Chemical Technology*, 5th ed. New York: John Wiley & Sons, 16:1–28.

Anttila A, Pukkala E, Aitio A *et al.* (1998). Update of cancer incidence among workers at a copper/nickel smelter and nickel refinery. *Int Arch Occup Environ Health*, 71: 245–250. doi:10.1007/s004200050276 PMID:9638480

Arena VC, Sussman NB, Redmond CK *et al.* (1998). Using alternative comparison populations to assess occupation-related mortality risk. Results for the high nickel alloys workers cohort. *J Occup Environ Med*, 40: 907–916. doi:10.1097/00043764-199810000-00012 PMID:9800177

Arrouijal FZ, Hildebrand HF, Vophi H, Marzin D (1990). Genotoxic activity of nickel subsulphide alpha-Ni3S2. *Mutagenesis*, 5: 583–589. doi:10.1093/mutage/5.6.583 PMID:2263215

Arrouijal FZ, Marzin D, Hildebrand HF *et al.* (1992). Differences in genotoxic activity of alpha-Ni3S2 on human lymphocytes from nickel-hypersensitized and nickel-unsensitized donors. *Mutagenesis*, 7: 183–187. doi:10.1093/mutage/7.3.183 PMID:1602972

Asmuss M, Mullenders LH, Eker A, Hartwig A (2000a). Differential effects of toxic metal compounds on the activities of Fpg and XPA, two zinc finger proteins involved in DNA repair. *Carcinogenesis*, 21: 2097–2104. doi:10.1093/carcin/21.11.2097 PMID:11062174

Asmuss M, Mullenders LH, Hartwig A (2000b). Interference by toxic metal compounds with isolated zinc finger DNA repair proteins. *Toxicol Lett*, 112–113: 227–231. doi:10.1016/S0378-4274(99)00273-8 PMID:10720735

ATSDR (2005). *Toxicological Profile for Nickel.* Atlanta, GA: US Public Health Service, Agency for Toxic Substances and Disease Registry.

Barbante C, Boutron C, Moreau A-L *et al.* (2002). Seasonal variations in nickel and vanadium in Mont Blanc snow and ice dated from the 1960s and 1990s. *J Environ Monit*, 4: 960–966. doi:10.1039/b208142c PMID:12509051

Basketter DA, Angelini G, Ingber A *et al.* (2003). Nickel, chromium and cobalt in consumer products: revisiting safe levels in the new millennium. *Contact Dermatitis*, 49: 1–7. doi:10.1111/j.0105-1873.2003.00149.x PMID:14641113

Bavazzano P, Bolognesi R, Cassinelli C *et al.* (1994). Skin contamination and low airborne nickel exposure of electroplaters. *Sci Total Environ*, 155: 83–86. PMID:7973613

Benson JM, Barr EB, Bechtold HA *et al.* (1994). Fate of Inhaled Nickel Oxide and Nickel Subsulfide in F344/N Rats. *Inhal Toxicol*, 6: 167–183. doi:10.3109/08958379409029703

Benson JM, Chang IY, Cheng YS *et al.* (1995a). Particle clearance and histopathology in lungs of F344/N rats and B6C3F1 mice inhaling nickel oxide or nickel sulfate. *Fundam Appl Toxicol*, 28: 232–244. doi:10.1006/faat.1995.1164 PMID:8835233

Benson JM, Cheng YS, Eidson AF *et al.* (1995b). Pulmonary toxicity of nickel subsulfide in F344/N rats exposed for 1–22 days. *Toxicology*, 103: 9–22. doi:10.1016/0300-483X(95)03098-Z PMID:8525492

Bernacki EJ, Parsons GE, Roy BR *et al.* (1978). Urine nickel concentrations in nickel-exposed workers. *Ann Clin Lab Sci*, 8: 184–189. PMID:655606

Berry JP, Galle P, Poupon MF *et al.* (1984). Electron microprobe in vitro study of interaction of carcinogenic nickel compounds with tumour cells. *IARC Sci Publ*, 53153–164. PMID:6099827

Beyersmann D & Hartwig A (2008). Carcinogenic metal compounds: recent insight into molecular and cellular

mechanisms. *Arch Toxicol*, 82: 493–512. doi:10.1007/s00204-008-0313-y PMID:18496671

Błasiak J, Arabski M, Pertyński T *et al.* (2002). DNA damage in human colonic mucosa cells evoked by nickel and protective action of quercetin - involvement of free radicals? *Cell Biol Toxicol*, 18: 279–288. doi:10.1023/A:1016059112829 PMID:12206140

Burges DCL (1980). *Mortality study of nickel platers*. In: *Nickel Toxicology*. Brown, S.S. & Sunderman, F.W., Jr, editors. London: Academic Press, pp. 1–18.

Cai Y & Zhuang Z (1999). DNA damage in human peripheral blood lymphocyte caused by nickel and cadmium *Zhonghua Yu Fang Yi Xue Za Zhi*, 33: 75–77. PMID:11864456

Caicedo M, Jacobs JJ, Reddy A *et al.* (2007). Analysis of metal ion-induced DNA damage, apoptosis, and necrosis in human (Jurkat) T-cells demonstrates Ni(2+) and V(3+) are more toxic than other metals: Al(3+), Be(2+), Co(2+), Cr(3+), Cu(2+), Fe(3+), Mo(5+), Nb(5+), Zr(2+). *J Biomed Mater Res A*, 86: 905–913.

CAREX Canada (2011). Available at: http://www.carexcanada.ca/en/nickel/occupational_exposure_estimates/phase_2/

Chakrabarti SK, Bai C, Subramanian KS (2001). DNA-protein crosslinks induced by nickel compounds in isolated rat lymphocytes: role of reactive oxygen species and specific amino acids. *Toxicol Appl Pharmacol*, 170: 153–165. doi:10.1006/taap.2000.9097 PMID:11162780

Chen CY, Wang YF, Huang WR, Huang YT (2003). Nickel induces oxidative stress and genotoxicity in human lymphocytes. *Toxicol Appl Pharmacol*, 189: 153–159. doi:10.1016/S0041-008X(03)00086-3 PMID:12791300

Chen H, Ke Q, Kluz T *et al.* (2006). Nickel ions increase histone H3 lysine 9 dimethylation and induce transgene silencing. *Mol Cell Biol*, 26: 3728–3737. doi:10.1128/MCB.26.10.3728-3737.2006 PMID:16648469

Conway K & Costa M (1989). Nonrandom chromosomal alterations in nickel-transformed Chinese hamster embryo cells. *Cancer Res*, 49: 6032–6038. PMID:2790817

Conway K, Wang XW, Xu LS, Costa M (1987). Effect of magnesium on nickel-induced genotoxicity and cell transformation. *Carcinogenesis*, 8: 1115–1121. doi:10.1093/carcin/8.8.1115 PMID:3301046

Costa M, Davidson TL, Chen H *et al.* (2005). Nickel carcinogenesis: epigenetics and hypoxia signalling. *Mutat Res*, 592: 79–88. PMID:16009382

Costa M, Yan Y, Zhao D, Salnikow K (2003). Molecular mechanisms of nickel carcinogenesis: gene silencing by nickel delivery to the nucleus and gene activation/inactivation by nickel-induced cell signalling. *J Environ Monit*, 5: 222–223. doi:10.1039/b210260a PMID:12729258

Cox JE, Doll R, Scott WA, Smith S (1981). Mortality of nickel workers: experience of men working with metallic nickel. *Br J Ind Med*, 38: 235–239. PMID:7272235

Cragle DL, Hollis DR, Newport TH, Shy CM (1984). A retrospective cohort mortality study among workers occupationally exposed to metallic nickel powder at the Oak Ridge Gaseous Diffusion Plant. *IARC Sci Publ*, 5357–63. PMID:6532993

Creely KS, Aitken RJ (2008). Characterization of nickel industry workplace aerosols by particle size and nickel species. Research Report TM/07/03. January 2008. Edinburgh: Institute of Occupational Medicine

Dally H & Hartwig A (1997). Induction and repair inhibition of oxidative DNA damage by nickel(II) and cadmium(II) in mammalian cells. *Carcinogenesis*, 18: 1021–1026. doi:10.1093/carcin/18.5.1021 PMID:9163690

Dhir H, Agarwal K, Sharma A, Talukder G (1991). Modifying role of Phyllanthus emblica and ascorbic acid against nickel clastogenicity in mice. *Cancer Lett*, 59: 9–18. doi:10.1016/0304-3835(91)90129-6 PMID:1878862

Diwan BA, Kasprzak KS, Rice JM (1992). Transplacental carcinogenic effects of nickel(II) acetate in the renal cortex, renal pelvis and adenohypophysis in F344/NCr rats. *Carcinogenesis*, 13: 1351–1357. doi:10.1093/carcin/13.8.1351 PMID:1499087

Dunnick JK, Elwell MR, Radovsky AE *et al.* (1995). Comparative carcinogenic effects of nickel subsulfide, nickel oxide, or nickel sulfate hexahydrate chronic exposures in the lung. *Cancer Res*, 55: 5251–5256. PMID:7585584

Durham TR & Snow ET (2006). Metal ions and carcinogenesis. *EXS*, 96: 97–130. PMID:16383016

Easton DF, Peto J, Morgan LG *et al.* (1992). *Respiratory cancer mortality in Welsh nickel refiners: Which nickel compounds are responsible?* In: *Nickel and human health: current perspectives. Advances in environmental sciences and technology*. Niebor E, Nrigau J, editors. New York: Wiley & Sons, pp. 603–619.

Edwards DL, Wataha JC, Hanks CT (1998). Uptake and reversibility of uptake of nickel by human macrophages. *J Oral Rehabil*, 25: 2–7. doi:10.1046/j.1365-2842.1998.00197.x PMID:9502120

Egedahl R, Carpenter M, Lundell D (2001). Mortality experience among employees at a hydrometallurgical nickel refinery and fertiliser complex in Fort Saskatchewan, Alberta (1954–95). *Occup Environ Med*, 58: 711–715. doi:10.1136/oem.58.11.711 PMID:11600726

Enterline PE & Marsh GM (1982). Mortality among workers in a nickel refinery and alloy manufacturing plant in West Virginia. *J Natl Cancer Inst*, 68: 925–933. PMID:6953273

EVM (2002). *Expert Group on Vitamins and Minerals: Revised Review of Nickel. EVM/99/24.*

Fletcher GG, Rossetto FE, Turnbull JD, Nieboer E (1994). Toxicity, uptake, and mutagenicity of particulate and

soluble nickel compounds. *Environ Health Perspect*, 102: Suppl 369–79. doi:10.2307/3431766 PMID:7843140

Funakoshi T, Inoue T, Shimada H, Kojima S (1997). The mechanisms of nickel uptake by rat primary hepatocyte cultures: role of calcium channels. *Toxicology*, 124: 21–26. doi:10.1016/S0300-483X(97)00131-5 PMID:9392452

Furst A & Schlauder MC (1971). The hamster as a model for metal carcinogenesis. *Proc West Pharmacol Soc*, 14: 68–71.

Garrick MD, Singleton ST, Vargas F *et al.* (2006). DMT1: which metals does it transport? *Biol Res*, 39: 79–85. doi:10.4067/S0716-97602006000100009 PMID:16629167

Gilman JP (1962). Metal carcinogenesis. II. A study on the carcinogenic activity of cobalt, copper, iron, and nickel compounds. *Cancer Res*, 22: 158–162. PMID:13898693

Gilman JP (1966). Muscle tumourigenesis. *Proc Can Cancer Conf*, 6: 209–223. PMID:5972980

Godbold JH Jr & Tompkins EA (1979). A long-term mortality study of workers occupationally exposed to metallic nickel at the Oak Ridge Gaseous Diffusion Plant. *J Occup Med*, 21: 799–806. PMID:556270

Goldberg M, Goldberg P, Leclerc A *et al.* (1994). A 10-year incidence survey of respiratory cancer and a case-control study within a cohort of nickel mining and refining workers in New Caledonia. *Cancer Causes Control*, 5: 15–25. doi:10.1007/BF01830722 PMID:8123774

Golebiowski F & Kasprzak KS (2005). Inhibition of core histones acetylation by carcinogenic nickel(II). *Mol Cell Biochem*, 279: 133–139. doi:10.1007/s11010-005-8285-1 PMID:16283522

Grimsrud TK, Berge SR, Haldorsen T, Andersen A (2002). Exposure to different forms of nickel and risk of lung cancer. *Am J Epidemiol*, 156: 1123–1132. doi:10.1093/aje/kwf165 PMID:12480657

Grimsrud TK, Berge SR, Haldorsen T, Andersen A (2005). Can lung cancer risk among nickel refinery workers be explained by occupational exposures other than nickel? *Epidemiologyl*, 16: 146–154. doi:10.1097/01.ede.0000152902.48916.d7 PMID:15703528

Grimsrud TK, Berge SR, Martinsen JI, Andersen A (2003). Lung cancer incidence among Norwegian nickel-refinery workers 1953–2000. *J Environ Monit*, 5: 190–197. doi:10.1039/b211722n PMID:12729252

Grimsrud TK, Berge SR, Resmann SR *et al.* (2000). Assessment of historical exposures in a nickel refinery in Norway. *Scand J Work Environ Health*, 26: 338–345. PMID:10994800

Grimsrud TK & Peto J (2006). Persisting risk of nickel related lung cancer and nasal cancer among Clydach refiners. *Occup Environ Med*, 63: 365–366. doi:10.1136/oem.2005.026336 PMID:16621856

Gunshin H, Mackenzie B, Berger UV *et al.* (1997). Cloning and characterization of a mammalian proton-coupled metal-ion transporter. *Nature*, 388: 482–488. doi:10.1038/41343 PMID:9242408

Harmse JL & Engelbrecht JC (2007). Air sampling of nickel in a refinery. *Int J Environ Health Res*, 17: 319–325. doi:10.1080/09603120701372698 PMID:17613095

Harris GK & Shi X (2003). Signaling by carcinogenic metals and metal-induced reactive oxygen species. *Mutat Res*, 533: 183–200. PMID:14643420

Hartmann M & Hartwig A (1998). Disturbance of DNA damage recognition after UV-irradiation by nickel(II) and cadmium(II) in mammalian cells. *Carcinogenesis*, 19: 617–621. doi:10.1093/carcin/19.4.617 PMID:9600346

Hartwig A, Asmuss M, Ehleben I *et al.* (2002). Interference by toxic metal ions with DNA repair processes and cell cycle control: molecular mechanisms. *Environ Health Perspect*, 110: Suppl 5797–799. PMID:12426134

Hartwig A & Beyersmann D (1989). Enhancement of UV-induced mutagenesis and sister-chromatid exchanges by nickel ions in V79 cells: evidence for inhibition of DNA repair. *Mutat Res*, 217: 65–73. PMID:2911267

Hartwig A, Mullenders LH, Schlepegrell R *et al.* (1994). Nickel(II) interferes with the incision step in nucleotide excision repair in mammalian cells. *Cancer Res*, 54: 4045–4051. PMID:8033135

Heath JC & Daniel MR (1964). The production of malignant tumours by cadmium in the rat. *Br J Cancer*, 18: 124–129. PMID:14154225

Heim KE, Bates HK, Rush RE, Oller AR (2007). Oral carcinogenicity study with nickel sulfate hexahydrate in Fischer 344 rats. *Toxicol Appl Pharmacol*, 224: 126–137. doi:10.1016/j.taap.2007.06.024 PMID:17692353

Hildebrand HF, D'Hooghe MC, Shirali P *et al.* (1990). Uptake and biological transformation of beta NiS and alpha Ni3S2 by human embryonic pulmonary epithelial cells (L132) in culture. *Carcinogenesis*, 11: 1943–1950. doi:10.1093/carcin/11.11.1943 PMID:2225326

Hildebrand HF, Decaestecker AM, Arrouijal FZ, Martinez R (1991). In vitro and in vivo uptake of nickel sulfides by rat lymphocytes. *Arch Toxicol*, 65: 324–329. doi:10.1007/BF01968967 PMID:1953351

Hong YC, Paik SR, Lee HJ *et al.* (1997). Magnesium inhibits nickel-induced genotoxicity and formation of reactive oxygen. *Environ Health Perspect*, 105: 744–748. doi:10.2307/3433730 PMID:9294721

Horn-Ross PL, Ljung B-M, Morrow M (1997). Environmental factors and the risk of salivary gland cancer. *Epidemiol.*, 8: 414–419. doi:10.1097/00001648-199707000-00011 PMID:9209856

Howard W, Leonard B, Moody W, Kochhar TS (1991). Induction of chromosome changes by metal compounds in cultured CHO cells. *Toxicol Lett*, 56: 179–186. doi:10.1016/0378-4274(91)90105-F PMID:2017776

Huang X, Frenkel K, Klein CB, Costa M (1993). Nickel induces increased oxidants in intact cultured mammalian cells as detected by dichlorofluorescein

fluorescence. *Toxicol Appl Pharmacol*, 120: 29–36. doi:10.1006/taap.1993.1083 PMID:8511780

Hueper WC (1952). Experimental studies in metal cancerigenesis. I. Nickel cancers in rats. *Tex Rep Biol Med*, 10: 167–186. PMID:14922272

Hueper WC (1955). Experimental studies in metal cancerigenesis. IV. Cancer produced by parenterally introduced metallic nickel. *J Natl Cancer Inst*, 16: 55–73. PMID:13243113

IARC (1973). Some inorganic and organometallic compounds. *IARC Monogr Eval Carcinog Risk Chem Man*, 2: 1–181.

IARC (1976). Cadmium, nickel, some epoxides, miscellaneous industrial chemicals and general considerations on volatile anaesthetics. *IARC Monogr Eval Carcinog Risk Chem Man*, 11: 1–306. PMID:992654

IARC (1979). Chemicals and industrial processes associated with cancer in humans: IARC Monographs volumes 1 to 20. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 1: 38

IARC (1982). Cross index of synonyms and trade names in Volumes 1 to 26. *IARC Monogr Eval Carcinog Risk Chem Hum Suppl*, 3: 1–199. PMID:6959964

IARC (1987). Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. *IARC Monogr Eval Carcinog Risks Hum Suppl*, 7: 264–269. PMID:3482203

IARC (1990). Chromium, nickel and welding. *IARC Monogr Eval Carcinog Risks Hum*, 49: 1–648. PMID:2232124

International Committee on Nickel Carcinogenesis in Man. (1990). Report of the International Committee on Nickel Carcinogenesis in Man. *Scand J Work Environ Health*, 16: 1 Spec No1–82. PMID:2185539

Iwitzki F, Schlepegrell R, Eichhorn U *et al.* (1998). Nickel(II) inhibits the repair of O6-methylguanine in mammalian cells. *Arch Toxicol*, 72: 681–689. doi:10.1007/s002040050561 PMID:9879805

Järup L, Bellander T, Hogstedt C, Spång G (1998). Mortality and cancer incidence in Swedish battery workers exposed to cadmium and nickel. *Occup Environ Med*, 55: 755–759. PMID:9924452

Jasmin G & Riopelle JL (1976). Renal carcinomas and erythrocytosis in rats following intrarenal injection of nickel subsulfide. *Lab Invest*, 35: 71–78. PMID:940323

Judde JG, Breillout F, Clemenceau C *et al.* (1987). Inhibition of rat natural killer cell function by carcinogenic nickel compounds: preventive action of manganese. *J Natl Cancer Inst*, 78: 1185–1190. PMID:2438444

Karaczyn AA, Golebiowski F, Kasprzak KS (2006). Ni(II) affects ubiquitination of core histones H2B and H2A. *Exp Cell Res*, 312: 3252–3259. doi:10.1016/j.yexcr.2006.06.025 PMID:16870173

Karjalainen S, Kerttula R, Pukkala E (1992). Cancer risk among workers at a copper/nickel smelter and nickel refinery in Finland. *Int Arch Occup Environ Health*, 63: 547–551. doi:10.1007/BF00386344 PMID:1587630

Kasprzak KS, Diwan BA, Konishi N *et al.* (1990). Initiation by nickel acetate and promotion by sodium barbital of renal cortical epithelial tumors in male F344 rats. *Carcinogenesis*, 11: 647–652. doi:10.1093/carcin/11.4.647 PMID:2323003

Kasprzak KS, Diwan BA, Rice JM (1994). Iron accelerates while magnesium inhibits nickel-induced carcinogenesis in the rat kidney. *Toxicology*, 90: 129–140. doi:10.1016/0300-483X(94)90211-9 PMID:8023338

Kasprzak KS, Gabryel P, Jarczewska K (1983). Carcinogenicity of nickel(II)hydroxides and nickel(II) sulfate in Wistar rats and its relation to the in vitro dissolution rates. *Carcinogenesis*, 4: 275–279. doi:10.1093/carcin/4.3.275 PMID:6831634

Kasprzak KS, Jaruga P, Zastawny TH *et al.* (1997). Oxidative DNA base damage and its repair in kidneys and livers of nickel(II)-treated male F344 rats. *Carcinogenesis*, 18: 271–277. doi:10.1093/carcin/18.2.271 PMID:9054618

Kasprzak KS, Sunderman FW Jr, Salnikow K (2003). Nickel carcinogenesis. *Mutat Res*, 533: 67–97. PMID:14643413

Kasprzak KS & Ward JM (1991). Prevention of nickel subsulfide carcinogenesis by local administration of Mycobacterium bovis antigen in male F344/NCr rats. *Toxicology*, 67: 97–105. doi:10.1016/0300-483X(91)90167-Y PMID:2017766

Kawanishi S, Inoue S, Oikawa S *et al.* (2001). Oxidative DNA damage in cultured cells and rat lungs by carcinogenic nickel compounds. *Free Radic Biol Med*, 31: 108–116. doi:10.1016/S0891-5849(01)00558-5 PMID:11425496

Kawanishi S, Oikawa S, Inoue S, Nishino K (2002). Distinct mechanisms of oxidative DNA damage induced by carcinogenic nickel subsulfide and nickel oxides. *Environ Health Perspect*, 110: Suppl 5789–791. PMID:12426132

Ke Q, Davidson T, Chen H *et al.* (2006). Alterations of histone modifications and transgene silencing by nickel chloride. *Carcinogenesis*, 27: 1481–1488. doi:10.1093/carcin/bgl004 PMID:16522665

Ke Q, Davidson T, Kluz T *et al.* (2007). Fluorescent tracking of nickel ions in human cultured cells. *Toxicol Appl Pharmacol*, 219: 18–23. doi:10.1016/j.taap.2006.08.013 PMID:17239912

Ke Q, Ellen TP, Costa M (2008a). Nickel compounds induce histone ubiquitination by inhibiting histone deubiquitinating enzyme activity. *Toxicol Appl Pharmacol*, 228: 190–199. doi:10.1016/j.taap.2007.12.015 PMID:18279901

Ke Q, Li Q, Ellen TP *et al.* (2008b). Nickel compounds induce phosphorylation of histone H3 at serine 10 by activating JNK-MAPK pathway. *Carcinogenesis*, 29: 1276–1281. doi:10.1093/carcin/bgn084 PMID:18375956

Kerfoot DGE (2002). *Nickel*. In: *Ullmann's Encyclopedia of Industrial Chemistry*. Wiley-VCH Verlag GmbH & Co.

Kiilunen M (1997). Occupational exposure to chromium and nickel in the 1980s in Finland. *Sci Total Environ*, 199: 91–101. doi:10.1016/S0048-9697(97)05484-3 PMID:9200851

Kiilunen M, Utela J, Rantanen T *et al.* (1997). Exposure to soluble nickel in electrolytic nickel refining. *Ann Occup Hyg*, 41: 167–188. PMID:9155238

Kuck PH (2008). *Nickel.* In: *Mineral commodity summaries*. Reston, VA, US Geological Survey. Ref Type: Report

Kuehn K, Fraser CB, Sunderman FW Jr (1982). Phagocytosis of particulate nickel compounds by rat peritoneal macrophages in vitro. *Carcinogenesis*, 3: 321–326. doi:10.1093/carcin/3.3.321 PMID:7083473

Lee YW, Klein CB, Kargacin B *et al.* (1995). Carcinogenic nickel silences gene expression by chromatin condensation and DNA methylation: a new model for epigenetic carcinogens. *Mol Cell Biol*, 15: 2547–2557. PMID:7537850

Lee-Chen SF, Wang MC, Yu CT *et al.* (1993). Nickel chloride inhibits the DNA repair of UV-treated but not methyl methanesulfonate-treated Chinese hamster ovary cells. *Biol Trace Elem Res*, 37: 39–50. doi:10.1007/BF02789400 PMID:7682828

Leikauf GD (2002). Hazardous air pollutants and asthma. *Environ Health Perspect*, 110: Suppl 4505–526. PMID:12194881

Lin X & Costa M (1994). Transformation of human osteoblasts to anchorage-independent growth by insoluble nickel particles. *Environ Health Perspect*, 102: Suppl 3289–292. doi:10.2307/3431804 PMID:7843117

Little JB, Frenial JM, Coppey J (1988). Studies of mutagenesis and neoplastic transformation by bivalent metal ions and ionizing radiation. *Teratog Carcinog Mutagen*, 8: 287–292. doi:10.1002/tcm.1770080505 PMID:2905837

Lu H, Shi X, Costa M, Huang C (2005). Carcinogenic effect of nickel compounds. *Mol Cell Biochem*, 279: 45–67. doi:10.1007/s11010-005-8215-2 PMID:16283514

M'Bemba-Meka P, Lemieux N, Chakrabarti SK (2005). Nickel compound-induced DNA single-strand breaks in chromosomal and nuclear chromatin in human blood lymphocytes in vitro: role of oxidative stress and intracellular calcium. *Mutat Res*, 586: 124–137. PMID:16099703

M'Bemba-Meka P, Lemieux N, Chakrabarti SK (2007). Role of oxidative stress and intracellular calcium in nickel carbonate hydroxide-induced sister-chromatid exchange, and alterations in replication index and mitotic index in cultured human peripheral blood lymphocytes. *Arch Toxicol*, 81: 89–99. doi:10.1007/s00204-006-0128-7 PMID:16826409

Madrid L, Diaz-Barrientos E, Ruiz-Cortés E *et al.* (2006). Variability in concentrations of potentially toxic elements in urban parks from six European cities. *J Environ Monit*, 8: 1158–1165. doi:10.1039/b607980f PMID:17075623

Magnus K, Andersen A, Høgetveit AC (1982). Cancer of respiratory organs among workers at a nickel refinery in Norway. *Int J Cancer*, 30: 681–685. PMID:7160938

McNeill DA, Chrisp CE, Fisher GL (1990). Tumorigenicity of nickel subsulfide in Strain A/J mice. *Drug Chem Toxicol*, 13: 71–86. doi:10.3109/01480549009011070 PMID:2379474

Minoia C, Sabbioni E, Apostoli P *et al.* (1990). Trace element reference values in tissues from inhabitants of the European community. I. A study of 46 elements in urine, blood and serum of Italian subjects. *Sci Total Environ*, 95: 89–105. doi:10.1016/0048-9697(90)90055-Y PMID:2402627

Mitchell DF, Shankwalker GB, Shazer S (1960). Determining the tumorigenicity of dental materials. *J Dent Res*, 39: 1023–1028. doi:10.1177/00220345600390050401 PMID:13771327

Miura T, Patierno SR, Sakuramoto T, Landolph JR (1989). Morphological and neoplastic transformation of C3H/10T1/2 Cl 8 mouse embryo cells by insoluble carcinogenic nickel compounds. *Environ Mol Mutagen*, 14: 65–78. doi:10.1002/em.2850140202 PMID:2548861

Moulin JJ, Clavel T, Roy D *et al.* (2000). Risk of lung cancer in workers producing stainless steel and metallic alloys. *Int Arch Occup Environ Health*, 73: 171–180. PMID:10787132

Moulin JJ, Lafontaine M, Mantout B *et al.* (1995). Mortality due to bronchopulmonary cancers in workers of 2 foundries *Rev Epidemiol Sante Publique*, 43: 107–121. PMID:7732197

Moulin JJ, Portefaix P, Wild P *et al.* (1990). Mortality study among workers producing ferroalloys and stainless steel in France. *Br J Ind Med*, 47: 537–543. PMID:2393634

Moulin JJ, Wild P, Haguenoer JM *et al.* (1993b). A mortality study among mild steel and stainless steel welders. *Br J Ind Med*, 50: 234–243. PMID:8457490

Moulin JJ, Wild P, Mantout B *et al.* (1993a). Mortality from lung cancer and cardiovascular diseases among stainless-steel producing workers. *Cancer Causes Control*, 4: 75–81. PMID:8386949

Nackerdien Z, Kasprzak KS, Rao G *et al.* (1991). Nickel(II)- and cobalt(II)-dependent damage by hydrogen peroxide to the DNA bases in isolated human chromatin. *Cancer Res*, 51: 5837–5842. PMID:1933852

National Institute for Occupational Safety and Health (NIOSH) (1990) *National Occupational Exposure Survey.*

NTP (1996a). *NTP Toxicology and Carcinogenesis Studies of Nickel Sulfate Hexahydrate (CAS No. 10101–97–0) in F344 Rats and B6C3F1 Mice (Inhalation Studies)*, 454:1–380.

NTP (1996b). *NTP Toxicology and Carcinogenesis Studies of Nickel Subsulfide (CAS No. 12035–72–2) in F344 Rats and B6C3F1 Mice (Inhalation Studies)*, 453:1–365.

NTP (1996c). *NTP Toxicology and Carcinogenesis Studies of Nickel Oxide (CAS No. 1313–99–1) in F344 Rats and B6C3F1 Mice (Inhalation Studies)*, 451:1–381.

NTP (2000). *Final Report on Carcinogens Background Document for Metallic Nickel and Certain Nickel Alloys*. Research Triangle Park, NC.

Ohashi F, Fukui Y, Takada S *et al.* (2006). Reference values for cobalt, copper, manganese, and nickel in urine among women of the general population in Japan. *Int Arch Occup Environ Health*, 80: 117–126. doi:10.1007/s00420-006-0109-4 PMID:16736192

Ohmori T, Okada K, Terada M, Tabei R (1999). Low susceptibility of specific inbred colonies of rats to nickel tumorigenesis in soft tissue. *Cancer Lett*, 136: 53–58. doi:10.1016/S0304-3835(98)00308-5 PMID:10211939

Ohmori T, Uraga N, Komi K *et al.* (1990). The role of bone fracture at the site of carcinogen exposure on nickel carcinogenesis in the soft tissue. *Jpn J Cancer Res*, 81: 1247–1252. PMID:2125994

Ohshima S (2003). Induction of genetic instability and chromosomal instability by nickel sulfate in V79 Chinese hamster cells. *Mutagenesis*, 18: 133–137. doi:10.1093/mutage/18.2.133 PMID:12621068

Ojajärvi IA, Partanen TJ, Ahlbom A *et al.* (2000). Occupational exposures and pancreatic cancer: a meta-analysis. *Occup Environ Med*, 57: 316–324. doi:10.1136/oem.57.5.316 PMID:10769297

Oliveira JP, de Siqueira ME, da Silva CS (2000). Urinary nickel as bioindicator of workers' Ni exposure in a galvanizing plant in Brazil. *Int Arch Occup Environ Health*, 73: 65–68. doi:10.1007/PL00007940 PMID:10672494

Oller AR & Erexson G (2007). Lack of micronuclei formation in bone marrow of rats after repeated oral exposure to nickel sulfate hexahydrate. *Mutat Res*, 626: 102–110. PMID:17052950

Oller AR, Kirkpatrick DT, Radovsky A, Bates HK (2008). Inhalation carcinogenicity study with nickel metal powder in Wistar rats. *Toxicol Appl Pharmacol*, 233: 262–275. doi:10.1016/j.taap.2008.08.017 PMID:18822311

Ottolenghi AD, Haseman JK, Payne WW *et al.* (1975). Inhalation studies of nickel sulfide in pulmonary carcinogenesis of rats. *J Natl Cancer Inst*, 54: 1165–1172. PMID:165308

Oyabu T, Ogami A, Morimoto Y *et al.* (2007). Biopersistence of inhaled nickel oxide nanoparticles in rat lung. *Inhal Toxicol*, 19: Suppl 155–58. doi:10.1080/08958370701492995 PMID:17886051

Pang D, Burges DCL, Sorahan T (1996). Mortality study of nickel platers with special reference to cancers of the stomach and lung, 1945–93. *Occup Environ Med*, 53: 714–717. doi:10.1136/oem.53.10.714 PMID:8943838

Patierno SR, Dirscherl LA, Xu J (1993). Transformation of rat tracheal epithelial cells to immortal growth variants by particulate and soluble nickel compounds. *Mutat Res*, 300: 179–193. doi:10.1016/0165-1218(93)90049-J PMID:7687017

Poirier LA, Theiss JC, Arnold LJ, Shimkin MB (1984). Inhibition by magnesium and calcium acetates of lead subacetate- and nickel acetate-induced lung tumors in strain A mice. *Cancer Res*, 44: 1520–1522. PMID:6704965

Pool-Zobel BL, Lotzmann N, Knoll M *et al.* (1994). Detection of genotoxic effects in human gastric and nasal mucosa cells isolated from biopsy samples. *Environ Mol Mutagen*, 24: 23–45. doi:10.1002/em.2850240105 PMID:7519553

Pott F, Blome H, Bruch J *et al.* (1990). Einstufungsvorschlag für anorganische und organische Fasern. *Arbeitsmed Sozialmed Praventivmed*, 25: 463–466.

Pott F, Rippe RM, Roller M *et al.* (1989). *Tumours in the abdominal cavity of rats after intraperitoneal injection of nickel compounds*. In: *Proceedings of the International Conference on Heavy Metals in the Environment:12–15 September 1989*. Vernet JP, editor. Geneva: World Health Organization, pp. 127–129.

Pott F, Ziem U, Reiffer FJ *et al.* (1987). Carcinogenicity studies on fibres, metal compounds, and some other dusts in rats. *Exp Pathol*, 32: 129–152. PMID:3436395

Refsvik T & Andreassen T (1995). Surface binding and uptake of nickel(II) in human epithelial kidney cells: modulation by ionomycin, nicardipine and metals. *Carcinogenesis*, 16: 1107–1112. doi:10.1093/carcin/16.5.1107 PMID:7767972

Rodriguez RE, Misra M, Diwan BA *et al.* (1996). Relative susceptibilities of C57BL/6, (C57BL/6 x C3H/He) F1, and C3H/He mice to acute toxicity and carcinogenicity of nickel subsulfide. *Toxicology*, 107: 131–140. doi:10.1016/0300-483X(95)03251-A PMID:8599172

Rydh CJ & Svärd B (2003). Impact on global metal flows arising from the use of portable rechargeable batteries. *Sci Total Environ*, 302: 167–184. doi:10.1016/S0048-9697(02)00293-0 PMID:12526907

Salnikow K, Su W, Blagosklonny MV, Costa M (2000). Carcinogenic metals induce hypoxia-inducible factor-stimulated transcription by reactive oxygen species-independent mechanism. *Cancer Res*, 60: 3375–3378. PMID:10910041

Salnikow K & Zhitkovich A (2008). Genetic and epigenetic mechanisms in metal carcinogenesis and cocarcinogenesis: nickel, arsenic, and chromium. *Chem Res Toxicol*, 21: 28–44. doi:10.1021/tx700198a PMID:17970581

Schwerdtle T & Hartwig A (2006). Bioavailability and genotoxicity of soluble and particulate nickel compounds in cultured human lung cells. *Materialwiss Werkstofftech*, 37: 521–525. doi:10.1002/mawe.200600030

Seilkop S (2002). Occupational exposures and pancreatic cancer. *Occup Environ Med*, 58: 63––64. . doi:10.1136/oem.58.1.63a PMID:11216453

Seoane AI & Dulout FN (2001). Genotoxic ability of cadmium, chromium and nickel salts studied by kinetochore staining in the cytokinesis-blocked micronucleus assay. *Mutat Res*, 490: 99–106. PMID:11342235

Shirali P, Decaestecker AM, Marez T *et al.* (1991). Ni3S2 uptake by lung cells and its interaction with plasma membranes. *J Appl Toxicol*, 11: 279–288. doi:10.1002/jat.2550110409 PMID:1940002

Sivulka DJ (2005). Assessment of respiratory carcinogenicity associated with exposure to metallic nickel: a review. *Regul Toxicol Pharmacol*, 43: 117–133. PMID:16129532

Sivulka DJ & Seilkop SK (2009). Reconstruction of historical exposures in the US nickel alloy industry and the implications for carcinogenic hazard and risk assessments. *Regul Toxicol Pharmacol*, 53: 174–185. PMID:19545511

Skaug V, Gylseth B, Reiss ALP *et al.* (1985). *Tumor induction in rats after intrapleural injection of nickel subsulfide and nickel oxide*. In: *Progress in Nickel Toxicology*. Brown SS, Sunderman FWJ, editors. Oxford: Blackwell Scientific Publications, pp. 37–41.

Smith-Sivertsen T, Tchachtchine V, Lund E *et al.* (1998). Urinary nickel excretion in populations living in the proximity of two russian nickel refineries: a Norwegian-Russian population-based study. *Environ Health Perspect*, 106: 503–511. doi:10.1289/ehp.98106503 PMID:9681979

Snyder RD, Davis GF, Lachmann PJ (1989). Inhibition by metals of X-ray and ultraviolet-induced DNA repair in human cells. *Biol Trace Elem Res*, 21: 389–398. doi:10.1007/BF02917280 PMID:2484618

Sobti RC & Gill RK (1989). Incidence of micronuclei and abnormalities in the head of spermatozoa caused by the salts of a heavy metal, nickel. *Cytologia (Tokyo)*, 54: 249–253.

Sorahan T (2004). Mortality of workers at a plant manufacturing nickel alloys, 1958–2000. *Occup Med (Lond)*, 54: 28–34. doi:10.1093/occmed/kqg127 PMID:14963251

Sorahan T & Williams SP (2005). Mortality of workers at a nickel carbonyl refinery, 1958–2000. *Occup Environ Med*, 62: 80–85. doi:10.1136/oem.2004.014985 PMID:15657188

Stoner GD, Shimkin MB, Troxell MC *et al.* (1976). Test for carcinogenicity of metallic compounds by the pulmonary tumor response in strain A mice. *Cancer Res*, 36: 1744–1747. PMID:1268831

Stridsklev IC, Schaller K-H, Langård S (2007). Monitoring of chromium and nickel in biological fluids of grinders grinding stainless steel. *Int Arch Occup Environ Health*, 80: 450–454. doi:10.1007/s00420-006-0142-3 PMID:17051396

Sunderman FW Jr (1983). Organ and species specificity in nickel subsulfide carcinogenesis. *Basic Life Sci*, 24: 107–127. PMID:6860261

Sunderman FW Jr (1984). Carcinogenicity of nickel compounds in animals. *IARC Sci Publ*, 53: 127–142. PMID:6532978

Sunderman FW, Donnelly AJ, West B, Kincaid JF (1959). Nickel poisoning. IX. Carcinogenesis in rats exposed to nickel carbonyl. *AMA Arch Ind Health*, 20: 36–41. PMID:13660518

Sunderman FW Jr, Hopfer SM, Plowman MC, Knight JA (1990). Carcinogenesis bioassays of nickel oxides and nickel-copper oxides by intramuscular administration to Fischer-344 rats. *Res Commun Chem Pathol Pharmacol*, 70: 103–113. PMID:2263758

Sunderman FW, Kincaid JF, Donnelly AJ, West B (1957). Nickel poisoning. IV. Chronic exposure of rats to nickel carbonyl; a report after one year of observation. *AMA Arch Ind Health*, 16: 480–485. PMID:13478186

Sunderman FW Jr, Maenza RM, Hopfer SM *et al.* (1979). Induction of renal cancers in rats by intrarenal injection of nickel subsulfide. *J Environ Pathol Toxicol*, 2: 1511–1527. PMID:528855

Sunderman FW Jr & McCully KS (1983). Carcinogenesis tests of nickel arsenides, nickel antimonide, and nickel telluride in rats. *Cancer Invest*, 1: 469–474. doi:10.3109/07357908309020271 PMID:6667417

Sunderman FW Jr, McCully KS, Hopfer SM (1984). Association between erythrocytosis and renal cancers in rats following intrarenal injection of nickel compounds. *Carcinogenesis*, 5: 1511–1517. doi:10.1093/carcin/5.11.1511 PMID:6488475

Thomassen Y, Nieboer E, Romanova N *et al.* (2004). Multi-component assessment of worker exposures in a copper refinery. Part 1. Environmental monitoring. *J Environ Monit*, 6: 985–991. doi:10.1039/b408464k PMID:15568048

Tola S, Kilpiö J, Virtamo M (1979). Urinary and plasma concentrations of nickel as indicators of exposure to nickel in an electroplating shop. *J Occup Med*, 21: 184–188. PMID:438908

Tundermann JH, Tien JK, Howson TE (2005). *Nickel and nickel alloys*. In: *Kirk-Othmer Encyclopedia of Chemical Technology*. Volume 17. (online edition)

Uddin AN, Burns FJ, Rossman TG *et al.* (2007). Dietary chromium and nickel enhance UV-carcinogenesis in skin of hairless mice. *Toxicol Appl Pharmacol*, 221: 329–338. doi:10.1016/j.taap.2007.03.030 PMID:17499830

Ulrich L, Sulcová M, Špaček L *et al.* (1991). Investigation of professional nickel exposure in nickel refinery workers. *Sci Total Environ*, 101: 91–96. doi:10.1016/0048-9697(91)90106-O PMID:2057775

USGS (2008). *Nickel*. In: *2006 Minerals Yearbook*. Reston, VA: US Geological Survey.

Waalkes MP, Liu J, Kasprzak KS, Diwan BA (2004). Minimal influence of metallothionein over-expression on nickel carcinogenesis in mice. *Toxicol Lett*, 153: 357–364. doi:10.1016/j.toxlet.2004.06.003 PMID:15454311

Waalkes MP, Liu J, Kasprzak KS, Diwan BA (2005). Metallothionein-I/II double knockout mice are no more sensitive to the carcinogenic effects of nickel subsulfide than wild-type mice. *Int J Toxicol*, 24: 215–220. doi:10.1080/10915810591000668 PMID:16126615

Wang P, Guliaev AB, Hang B (2006). Metal inhibition of human N-methylpurine-DNA glycosylase activity in base excision repair. *Toxicol Lett*, 166: 237–247. doi:10.1016/j.toxlet.2006.06.647 PMID:16938414

WHO (2007). Nickel in Drinking Water. WHO/SDE/WSH/07.08/55. Geneva: World Health Organization

Woźniak K & Błasiak J (2002). Free radicals-mediated induction of oxidized DNA bases and DNA-protein cross-links by nickel chloride. *Mutat Res*, 514: 233–243. PMID:11815261

Woźniak K & Błasiak J (2004). Nickel impairs the repair of UV- and MNNG-damaged DNA. *Cell Mol Biol Lett*, 9: 83–94. PMID:15048153

Yarita T & Nettesheim P (1978). Carcinogenicity of nickel subsulfide for respiratory tract mucosa. *Cancer Res*, 38: 3140–3145. PMID:688205

Zhang Q, Salnikow K, Kluz T *et al.* (2003). Inhibition and reversal of nickel-induced transformation by the histone deacetylase inhibitor trichostatin A. *Toxicol Appl Pharmacol*, 192: 201–211. doi:10.1016/S0041-008X(03)00280-1 PMID:14575637

Zoroddu MA, Schinocca L, Kowalik-Jankowska T *et al.* (2002). Molecular mechanisms in nickel carcinogenesis: modeling Ni(II) binding site in histone H4. *Environ Health Perspect*, 110: Suppl 5719–723. PMID:12426119

ASBESTOS (CHRYSOTILE, AMOSITE, CROCIDOLITE, TREMOLITE, ACTINOLITE, AND ANTHOPHYLLITE)

Asbestos was considered by previous IARC Working Groups in 1972, 1976, and 1987 (IARC, 1973, 1977, 1987a). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

Asbestos is the generic commercial designation for a group of naturally occurring mineral silicate fibres of the serpentine and amphibole series. These include the serpentine mineral chrysotile (also known as 'white asbestos'), and the five amphibole minerals – actinolite, amosite (also known as 'brown asbestos'), anthophyllite, crocidolite (also known as 'blue asbestos'), and tremolite (IARC, 1973; USGS, 2001). The conclusions reached in this *Monograph* about asbestos and its carcinogenic risks apply to these six types of fibres wherever they are found, and that includes talc containing asbestiform fibres. Erionite (fibrous aluminosilicate) is evaluated in a separate *Monograph* in this volume.

Common names, Chemical Abstracts Service (CAS) Registry numbers and idealized chemical formulae for the six fibrous silicates designated as 'asbestos' are presented in Table 1.1. Specific chemical and physical properties are also presented.

1.2 Chemical and physical properties of the agent

The silicate tetrahedron (SiO_4) is the basic chemical unit of all silicate minerals. The number of tetrahedra in the crystal structure and how they are arranged determine how a silicate mineral is classified.

Serpentine silicates are classified as 'sheet silicates' because the tetrahedra are arranged to form sheets. Amphibole silicates are classified as 'chain silicates' because the tetrahedra are arranged to form a double chain of two rows aligned side by side. Magnesium is coordinated with the oxygen atom in serpentine silicates. In amphibole silicates, cationic elements such as aluminium, calcium, iron, magnesium, potassium, and sodium are attached to the tetrahedra. Amphiboles are distinguished from one another by their chemical composition. The chemical formulas of asbestos minerals are idealized. In

Table 1.1 Common names, CAS numbers, synonyms, non-asbestos mineral analogues, idealized chemical formulae, selected physical and chemical properties of asbestos minerals

Common Name	CAS No.	Synonyms	Non-Asbestos Mineral Analogue	Idealized Chemical Formula	Colour	Decomposition Temperature (°C)	Other Properties
Asbestos	1332-21-4*	Unspecified		Unspecified			
Serpentine group of minerals							
Chrysotile	12001-29-5*	Serpentine asbestos; white asbestos	Lizardite, antigorite	$[Mg_3Si_2O_5(OH)_4]_n$	White, grey, green, yellowish	600–850	Curled sheet silicate, hollow central core; fibre bundle lengths = several mm to more than 10 cm; fibres more flexible than amphiboles; net positive surface charge; forms a stable suspension in water; fibres degrade in dilute acids
Amphibole group of minerals							
Crocidolite	12001-28-4*	Blue asbestos	Riebeckite	$[NaFe^{2+}_3Fe^{3+}_2Si_8O_{22}(OH)_2]_n$	Lavender, blue green	400–900	Double chain silicate; shorter, thinner fibres than other amphiboles, but not as thin as chrysotile; fibre flexibility: fair to good; spinnability: fair; resistance to acids: good; less heat resistance than other asbestos fibres; usually contains organic impurities, including low levels of PAHs; negative surface charge in water
Amosite	12172-73-5*	Brown asbestos	Grunerite	$[(Mg,Fe^{2+})_7Si_8O_{22}(OH)_2]_n$	Brown, grey, greenish	600–900	Double chain silicate; long, straight, coarse fibres; fibre flexibility: somewhat; resistance to acids: somewhat; occurs with more iron than magnesium; negative surface charge in water
Anthophyllite	17068-78-9*	Ferroanthophyllite; azbolen asbestos	Anthophyllite	$[(Mg, Fe^{2+})_7Si_8O_{22}(OH)_2]_n$	Grey, white, brown-grey, green	NR	Double chain silicate; short, very brittle fibres; resistance to acids: very; relatively rare; occasionally occurs as contaminant in talc deposits; negative surface charge in water
Actinolite	12172-67-7*	Unspecified	Actinolite	$[Ca_2(Mg, Fe^{2+})_5Si_8O_{22}(OH)_2]_n$	Green	NR	Double chain silicate; brittle fibres; resistance to acids: none; occurs in asbestiform and non-asbestiform habit; iron-substituted derivative of tremolite; common contaminant in amosite deposits; negative surface charge in water
Tremolite	14567-73-8*	Silicic acid; calcium magnesium salt (8:4)	Tremolite	$[Ca_2Mg_5Si_8O_{22}(OH)_2]_n$	White to pale green	950–1040	Double chain silicate; brittle fibres; acid resistant; occurs in asbestiform and non-asbestiform habit; common contaminant in chrystotile and talc deposits; negative surface charge in water

* identified as asbestos by CAS Registry
NR, not reported
From ATSDR (2001), USGS (2001), HSE (2005), NTP (2005)

natural samples, the composition varies with respect to major and trace elements (USGS, 2001; HSE, 2005). More detailed information on the chemical and physical characteristics of asbestos – including atomic structure, crystal polytypes, fibre structure, chemistry and impurities – can be found in the previous *IARC Monograph* (IARC, 1973).

The structure of silicate minerals may be fibrous or non-fibrous. The terms 'asbestos' or 'asbestiform minerals' refer only to those silicate minerals that occur in polyfilamentous bundles, and that are composed of extremely flexible fibres with a relatively small diameter and a large length. These fibre bundles have splaying ends, and the fibres are easily separated from one another (USGS, 2001; HSE, 2005). Asbestos minerals with crystals that grow in two or three dimensions and that cleave into fragments, rather than breaking into fibrils, are classified as silicate minerals with a 'non-asbestiform' habit. These minerals may have the same chemical formula as the 'asbestiform' variety. (NIOSH, 2008).

Chrysotile, lizardite, and antigorite are the three principal serpentine silicate minerals. Of these, only chrysotile occurs in the asbestiform habit. Of the amphibole silicate minerals, amosite and crocidolite occur only in the asbestiform habit, while tremolite, actinolite and anthophyllite occur in both asbestiform and non-asbestiform habits (USGS, 2001; HSE, 2005; NTP, 2005).

Historically, there has been a lack of consistency in asbestos nomenclature. This frequently contributed to uncertainty in the specific identification of asbestos minerals reported in the literature. The International Mineralogical Association (IMA) unified the current mineralogical nomenclature under a single system in 1978. This system was subsequently modified in 1997 (NIOSH, 2008).

Asbestos fibres tend to possess good strength properties (e.g. high tensile strength, wear and friction characteristics); flexibility (e.g. the ability to be woven); excellent thermal properties (e.g. heat stability; thermal, electrical and acoustic insulation); adsorption capacity; and, resistance to chemical, thermal and biological degradation (USGS, 2001; NTP, 2005).

1.3 Use of the agent

Asbestos has been used intermittently in small amounts for thousands of years. Modern industrial use dates from about 1880, when the Quebec chrysotile fields began to be exploited. During the next 50 years gradual increases in production and use were reported with a cumulative total of somewhat less than 5000 million kg mined by 1930 (IARC, 1973).

As described above, asbestos has several chemical and physical properties that make it desirable for a wide range of industrial applications. By the time industrial and commercial use of asbestos peaked, more than 3000 applications or types of products were listed (NTP, 2005). Production and consumption of asbestos has declined in recent years due to the introduction of strict regulations governing exposure and/or outright bans on exposure.

Asbestos is used as a loose fibrous mixture, bonded with other materials (e.g. Portland cement, plastics and resins), or woven as a textile (ATSDR, 2001). The range of applications in which asbestos has been used includes: roofing, thermal and electrical insulation, cement pipe and sheets, flooring, gaskets, friction materials (e.g. brake pads and shoes), coating and compounds, plastics, textiles, paper, mastics, thread, fibre jointing, and millboard (USGS, 2001; NTP, 2005; Virta, 2006). Certain fibre characteristics, such as length and strength, are used to determine the most appropriate application. For example, longer fibres tend to be used in the production of textiles, electrical insulation, and filters; medium-length fibres are used in the production of asbestos cement pipes and sheets, friction materials (e.g. clutch facings, brake linings), gaskets, and pipe coverings; and,

short fibres are used to reinforce plastics, floor tiles, coatings and compounds, and roofing felts (NTP, 2005).

Since peaking in the 1970s, there has been a general decline in world production and consumption of asbestos. Peak world production was estimated to be 5.09 million metric tons in 1975, with approximately 25 countries producing asbestos and 85 countries manufacturing asbestos products (USGS, 2001; Nishikawa *et al.*, 2008). Worldwide 'apparent consumption' of asbestos (calculated as production plus imports minus exports) peaked at 4.73 million metric tons in 1980. Asbestos cement products are estimated to have accounted for 66% of world consumption in that year (Virta, 2006). In the USA, consumption of asbestos peaked in 1973 at 719000 metric tons (USGS, 2001).

Historical trends worldwide in per capita asbestos use are presented in Table 1.2, and peak use of asbestos was higher and occurred earlier in the countries of Northern and western Europe, Oceania, and the Americas (excluding South America). Very high asbestos use was recorded in Australia (5.1 kg per capita/year in the 1970s), Canada (4.4 kg per capita/year in the 1970s), and several countries of Northern and western Europe (Denmark: 4.8 kg per capita/year in the 1960s; Germany: 4.4 kg per capita/year in the 1970s; and Luxembourg: 5.5 kg per capita/year in the 1960s) (Nishikawa *et al.*, 2008).

Current use of asbestos varies widely. While some countries have imposed strict regulations to limit exposure and others have adopted bans, some have intervened less, and continue to use varying quantities of asbestos (Table 1.2). According to recent estimates by the US Geological Survey, world production of asbestos in 2007 was 2.20 million metric tonnes, slightly increased from 2.18 million metric ton in 2006. Six countries accounted for 96% of world production in 2006: the Russian Federation (925000 metric tons), the People's Republic of China (360000 metric tons), Kazakhstan (300000 metric tons), Brazil (227304 metric tons), Canada (185000 metric tons), and Zimbabwe (100000 metric tons) (Virta, 2008). During 2000–03, asbestos consumption increased in China, India, Kazakhstan, and the Ukraine (Virta, 2006). 'Apparent' world consumption of asbestos was 2.11 million metric tons in 2003, with the Russian Federation, several former Russian states and countries in Asia being the predominant users (Virta, 2006). Consumption of asbestos in the USA (predominantly chrysotile) was 2230 metric tons in 2006, declining to 1730 metric tons in 2007 (Virta, 2008). Roofing products (includes coatings and compounds) accounted for over 80% of asbestos consumption in the USA (Virta, 2008; Virta, 2009). Asbestos products were banned in all the countries of the European Union, including Member States of eastern Europe, effective January 1, 2005 (EU, 1999).

1.4 Environmental occurrence

1.4.1 Natural occurrence

Asbestos minerals are widespread in the environment, and are found in many areas where the original rock mass has undergone metamorphism (ATSDR, 2001; USGS, 2001). Examples include large chrysotile deposits in the Ural Mountains in the Russian Federation, in the Appalachian Mountains in the USA, and in Canada (Virta, 2006). They may occur in large natural deposits or as contaminants in other minerals (e.g. tremolite asbestos may occur in deposits of chrysotile, vermiculite, and talc). The most commonly occurring form of asbestos is chrysotile, and its fibres are found as veins in serpentine rock formations. Asbestiform amphiboles occur in relatively low quantities throughout the earth's crust and their chemical composition reflects the environment in which they form (Virta, 2002). Although most commercial deposits typically contain 5–6% of asbestos, a few deposits, such